



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification: C07D 239/94, A61K 31/517, A61P 35/00, C07D 215/54, C07D 401/12, C07D 405/12, C07D 413/12	A1	(11) International Publication Number: WO 00/55141 (43) International Publication Date: 21 September 2000 (21.09.2000)
(21) International Application Number: PCT/EP00/02228 (22) International Filing Date: 14 March 2000 (14.03.2000) (30) Priority Data: 199 11 509.5 15 March 1999 (15.03.1999) DE (60) Parent Application or Grant BOEHRINGER INGELHEIM PHARMA KG [/]; (). HIMMELSBACH, Frank [/]; (). LANGKOPF, Elke [/]; (). BLECH, Stefan [/]; (). JUNG, Birgit [/]; (). METZ, Thomas [/]; (). SOLCA, Flavio [/]; (). HIMMELSBACH, Frank [/]; (). LANGKOPF, Elke [/]; (). BLECH, Stefan [/]; (). JUNG, Birgit [/]; (). METZ, Thomas [/]; (). SOLCA, Flavio [/]; (). LAUDIEN, Dieter ; ().		Published
(54) Title: BICYCLIC HETEROCYCLES, PHARMACEUTICAL COMPOSITIONS CONTAINING THESE COMPOUNDS, AND PROCESSES FOR PREPARING THEM (54) Titre: HETEROCYCLES BICYCLIQUES, COMPOSITIONS PHARMACEUTIQUES CONTENANT CES COMPOSES, UTILISATIONS ET PROCEDES DE PREPARATION DE CES DERNIERS (57) Abstract <p>The present invention relates to bicyclic heterocyclic compounds of general formula (I), wherein R_{1a} to R_{1d}, A to D and X are defined as in claims 1 to 8, the tautomers, stereoisomers and salts thereof, particularly the physiologically acceptable salts thereof with inorganic or organic acids or bases which have valuable pharmacological properties, particularly an inhibitory effect on signal transduction mediated by tyrosine kinases, their use in treating diseases, particularly tumour diseases, diseases of the lung and airways and the preparation thereof.</p> (57) Abrégé <p>La présente invention concerne des composés hétérocycliques bicycliques de formule (I) dans laquelle R_{1a}, R_{1b}, R_{1c} et R_{1d}, A, B, C et D ainsi que X sont tels que définis dans les revendications 1 à 8, leurs tautomères, leurs stéréoisomères et leurs sels, plus particulièrement les sels physiologiquement acceptables de ces derniers associés à des acides ou des bases organiques ou inorganiques qui possèdent des propriétés pharmacologiques intéressantes, plus spécifiquement un effet inhibiteur sur la transduction du signal assisté par des tyrosine kinases, leur utilisation dans le traitement des maladies et plus particulièrement des maladies tumorales, des maladies pulmonaires et des voies aériennes ainsi que la préparation de ces composés.</p>		

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁷ : C07D 239/94, 215/54, 401/12, 413/12, 405/12, A61K 31/517, A61P 35/00		A1	(11) International Publication Number: WO 00/55141 (43) International Publication Date: 21 September 2000 (21.09.00)
(21) International Application Number: PCT/EP00/02228 (22) International Filing Date: 14 March 2000 (14.03.00) (30) Priority Data: 199 11 509.5 15 March 1999 (15.03.99) DE (71) Applicant (for all designated States except US): BOEHRINGER INGELHEIM PHARMA KG [DE/DE]; D-55216 Ingelheim/Rhein (DE). (72) Inventors; and (75) Inventors/Applicants (for US only): HIMMELSBACH, Frank [DE/DE]; Ahornweg 16, D-88441 Mittelbiberach (DE). LANGKOPF, Elke [DE/DE]; Im Schloss 3, D-88447 Warthausen (DE). BLECH, Stefan [DE/DE]; Müllerweg 9, D-88447 Warthausen (DE). JUNG, Birgit [DE/DE]; Mühlstrasse 23, D-55270 Schwabenheim (DE). METZ, Thomas [DE/AT]; Traungasse 6/5, A-1030 Vienna (AT). SOLCA, Flavio [CH/AT]; Fimbingerasse 1/9, A-1230 Vienna (AT). (74) Agent: LAUDIEN, Dieter; Boehringer Ingelheim GmbH, B Patente, D-55216 Ingelheim/Rhein (DE).		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.	
(54) Title: BICYCLIC HETEROCYCLES, PHARMACEUTICAL COMPOSITIONS CONTAINING THESE COMPOUNDS, AND PROCESSES FOR PREPARING THEM			
<div style="text-align: center;"> <p>(I)</p> </div>			
(57) Abstract <p>The present invention relates to bicyclic heterocyclic compounds of general formula (I), wherein R_a to R_d, A to D and X are defined as in claims 1 to 8, the tautomers, stereoisomers and salts thereof, particularly the physiologically acceptable salts thereof with inorganic or organic acids or bases which have valuable pharmacological properties, particularly an inhibitory effect on signal transduction mediated by tyrosine kinases, their use in treating diseases, particularly tumour diseases, diseases of the lung and airways and the preparation thereof.</p>			

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

Description

5

10

15

20

25

30

35

40

45

50

55

5

- 1 -

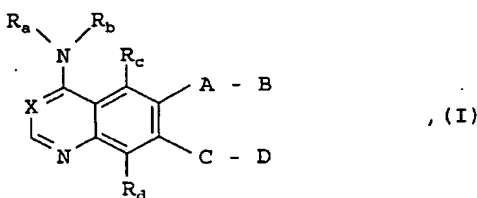
10

BICYCLIC HETEROCYCLES, PHARMACEUTICAL COMPOSITIONS CONTAINING THESE COMPOUNDS,
AND PROCESSES FOR PREPARING THEM

15

The present invention relates to bicyclic heterocyclic compounds of general formula

20



25

30

the tautomers, the stereoisomers and the salts thereof, particularly the physiologically acceptable salts thereof with inorganic or organic acids or bases which have valuable pharmacological properties, particularly an inhibiting effect on the signal transduction mediated by tyrosine kinases, their use in treating diseases, particularly tumoral diseases, diseases of the lungs and respiratory tract and the preparation thereof.

35

In the above general formula I

40

R_a denotes a hydrogen atom or a C₁₋₄-alkyl group,

R_b denotes a phenyl, benzyl or 1-phenylethyl group wherein the phenyl nucleus is substituted in each case by the groups R₁ to R₃, whilst

45

R₁ and R₂, which may be identical or different, each denote a hydrogen, fluorine, chlorine, bromine or iodine atom,

50

a C₁₋₄-alkyl, hydroxy, C₁₋₄-alkoxy, C₃₋₆-cycloalkyl, C₄₋₆-cycloalkoxy, C₂₋₅-alkenyl or C₂₋₅-alkynyl group,

55

an aryl, aryloxy, arylmethyl or arylmethoxy group,

a C₃₋₅-alkenyloxy or C₃₋₅-alkynyloxy group, whilst the unsaturated moiety may not be linked to the oxygen atom,

a C₁₋₄-alkylsulphenyl, C₁₋₄-alkylsulphinyl, C₁₋₄-alkylsulphonyl, C₁₋₄-alkylsulphonyloxy, trifluoromethylsulphenyl, trifluoromethylsulphinyl or trifluoromethylsulphonyl group,

a methyl or methoxy group substituted by 1 to 3 fluorine atoms,

an ethyl or ethoxy group substituted by 1 to 5 fluorine atoms,

a cyano or nitro group or an amino group optionally substituted by one or two C₁₋₄-alkyl groups, whilst the substituents may be identical or different,

or R₁ together with R₂, if they are bound to adjacent carbon atoms, denote a -CH=CH-CH=CH-, -CH=CH-NH or -CH=N-NH group and

R₃ denotes a hydrogen, fluorine, chlorine or bromine atom,

a C₁₋₄-alkyl, trifluoromethyl or C₁₋₄-alkoxy group,

R_c and R_d, which may be identical or different, each denote a hydrogen, fluorine or chlorine atom, a methoxy group or a methyl group optionally substituted by a methoxy, dimethylamino, diethylamino, pyrrolidino, piperidino or morpholino group,

X denotes a methine group substituted by a cyano group or a nitrogen atom,

A denotes an $-O-C_{1-6}$ -alkylene, $-O-C_{4-7}$ -cycloalkylene,
 ~~$-O-C_{1-3}$ -alkylene- C_{3-7} -cycloalkylene, $-O-C_{4-7}$ -cyclo-~~
~~alkylene- C_{1-3} -alkylene or $-O-C_{1-3}$ -alkylene- C_{3-7} -cycloal-~~
 kylene- C_{1-3} -alkylene group, whilst the oxygen atom of the
 abovementioned groups in each case is linked to the bicyclic
 heteroaromatic ring,

an $-O-C_{1-6}$ -alkylene group which is substituted by an R_6O-CO or
 $R_6O-CO-C_{1-4}$ -alkyl group, whilst R_6 is as hereinafter defined and
 the oxygen atom of the abovementioned $-O-C_{1-6}$ -alkylene groups in
 each case is linked to the bicyclic heteroaromatic ring,

an $-O-C_{2-6}$ -alkylene group which is substituted from position 2
 onwards by a hydroxy, C_{1-4} -alkoxy, amino, C_{1-4} -alkylamino, di-
 (C_{1-4} -alkyl)-amino, pyrrolidino, piperidino, morpholino, piper-
 azino or 4- (C_{1-4} -alkyl)-piperazino group and the oxygen atom of
 the abovementioned $-O-C_{2-6}$ -alkylene groups in each case is linked
 to the bicyclic heteroaromatic ring,

a $-C_{1-6}$ -alkylene group,

an $-NR_4-C_{1-6}$ -alkylene, $-NR_4-C_{3-7}$ -cycloalkylene, $-NR_4-C_{1-3}$ -alkylene-
 C_{3-7} -cycloalkylene, $-NR_4-C_{3-7}$ -cycloalkylene- C_{1-3} -alkylene or
 $-NR_4-C_{1-3}$ -alkylene- C_{3-7} -cycloalkylene- C_{1-3} -alkylene group, whilst
 the $-NR_4$ - moiety of the abovementioned groups in each case is
 linked to the bicyclic heteroaromatic ring, and

R_4 denotes a hydrogen atom or a C_{1-4} -alkyl group,

an oxygen atom, this being linked to a carbon atom of the
 group B, or

a NR_4 group, the latter being linked to a carbon atom of the
 group B and R_4 being as hereinbefore defined,

B denotes an R_6O-CO -alkylene- NR_5 , $(R_7O-PO-OR_6)$ -alkylene- NR_5 or
 $(R_7O-PO-R_6)$ -alkylene- NR_5 group wherein in each case the alkylene

moiety, which is straight-chained and contains 1 to 6 carbon atoms, may additionally be substituted by one or two C₁₋₂-alkyl groups or by an R₆O-CO or R₆O-CO-C₁₋₂-alkyl group, whilst

R₅ denotes a hydrogen atom,

a C₁₋₄-alkyl group which may be substituted by an R₆O-CO, (R₇O-PO-OR₈) or (R₇O-PO-R₉) group,

a C₂₋₄-alkyl group which is substituted from position 2 by a hydroxy, C₁₋₄-alkoxy, amino, C₁₋₄-alkylamino or di-(C₁₋₄-alkyl)-amino group or by a 4- to 7-membered alkyleneimino group, whilst in the abovementioned 6- to 7-membered alkyleneimino groups in each case a methylene group in the 4 position may be replaced by an oxygen or sulphur atom, by a sulphinyl, sulphonyl, imino or N-(C₁₋₄-alkyl)-imino group,

a C₃₋₇-cycloalkyl or C₃₋₇-cycloalkyl-C₁₋₃-alkyl group,

R₆, R₇ and R₈, which may be identical or different, in each case denote a hydrogen atom,

a C₁₋₈-alkyl group which may be substituted from position 2 onwards by a hydroxy, C₁₋₄-alkoxy, amino, C₁₋₄-alkylamino or di-(C₁₋₄-alkyl)-amino group or by a 4- to 7-membered alkyleneimino group, whilst in the abovementioned 6- to 7-membered alkyleneimino groups in each case a methylene group in the 4 position may be replaced by an oxygen or sulphur atom, by a sulphinyl, sulphonyl, imino or N-(C₁₋₄-alkyl)-imino group,

a C₄₋₇-cycloalkyl group optionally substituted by 1 or 2 methyl groups,

a C₃₋₅-alkenyl or C₃₋₅-alkynyl group, whilst the unsaturated moiety may not be linked to the oxygen atom,

- 5 -

a C₃₋₇-cycloalkyl-C₁₋₄-alkyl, aryl, aryl-C₁₋₄-alkyl or R₃CO-O-(R₆CR₇) group, whilst

R₆ and R₇, which may be identical or different, in each case denote a hydrogen atom or a C₁₋₄-alkyl group and

R₃ denotes a C₁₋₄-alkyl, C₃₋₇-cycloalkyl, C₁₋₄-alkoxy or C₅₋₇-cycloalkoxy group,

and R₅ denotes a C₁₋₄-alkyl, aryl or aryl-C₁₋₄-alkyl group,

a 4- to 7-membered alkyleneimino group which is substituted by an R₆O-CO, (R₇O-PO-OR₈), (R₇O-PO-R₉), R₆O-CO-C₁₋₄-alkyl, bis-(R₆O-CO)-C₁₋₄-alkyl, (R₇O-PO-OR₈)-C₁₋₄-alkyl or (R₇O-PO-R₉)-C₁₋₄-alkyl group wherein R₆ to R₉ are as hereinbefore defined,

a 4- to 7-membered alkyleneimino group which is substituted by two R₆O-CO or R₆O-CO-C₁₋₄-alkyl groups or by an R₆OCO group and an R₆O-CO-C₁₋₄-alkyl group wherein R₆ is as hereinbefore defined,

a piperazino or homopiperazino group which is substituted in the 4 position by the group R₁₀ and additionally at a cyclic carbon atom by an R₆O-CO, (R₇O-PO-OR₈), (R₇O-PO-R₉), R₆O-CO-C₁₋₄-alkyl, bis-(R₆O-CO)-C₁₋₄-alkyl, (R₇O-PO-OR₈)-C₁₋₄-alkyl or (R₇O-PO-R₉)-C₁₋₄-alkyl group wherein R₆ to R₉ are as hereinbefore defined and

R₁₀ denotes a hydrogen atom, a C₁₋₄-alkyl, formyl, C₁₋₄-alkylcarbonyl or C₁₋₄-alkylsulphonyl group,

a piperazino or homopiperazino group which is substituted in the 4 position by the group R₁₀ and is additionally substituted at cyclic carbon atoms by two R₆O-CO or R₆O-CO-C₁₋₄-alkyl groups or by an R₆O-CO group and an R₆O-CO-C₁₋₄-alkyl group wherein R₆ and R₁₀ are as hereinbefore defined,

5
a piperazino or homopiperazino group which is substituted in
each case in the 4 position by an $R_6O-CO-C_{1-4}$ -alkyl, bis-
10 $(R_6O-CO)-C_{1-4}$ -alkyl, $(R_7O-PO-OR_8)-C_{1-4}$ -alkyl or $(R_7O-PO-R_9)-C_{1-4}$ -alkyl group wherein R_6 to R_9 are as hereinbefore defined,

15 a piperazino or homopiperazino group which is substituted in
the 4 position by an $R_6O-CO-C_{1-4}$ -alkyl, bis- $(R_6O-CO)-C_{1-4}$ -alkyl,
 $(R_7O-PO-OR_8)-C_{1-4}$ -alkyl or $(R_7O-PO-R_9)-C_{1-4}$ -alkyl group and is
additionally substituted at cyclic carbon atoms by one or two
20 R_6O-CO or $R_6O-CO-C_{1-4}$ -alkyl groups or by an R_6O-CO group and an
 $R_6O-CO-C_{1-4}$ -alkyl group wherein R_6 to R_9 are as hereinbefore
defined,

25 a morpholino or homomorpholino group which is substituted in
each case by an R_6O-CO , $(R_7O-PO-OR_8)$, $(R_7O-PO-R_9)$, $R_6O-CO-C_{1-4}$ -al-
kyl, bis- $(R_6O-CO)-C_{1-4}$ -alkyl, $(R_7O-PO-OR_8)-C_{1-4}$ -alkyl or
 $(R_7O-PO-R_9)-C_{1-4}$ -alkyl group wherein R_6 to R_9 are as hereinbefore
defined,

30 a morpholino or homomorpholino group which is substituted by
two R_6O-CO or $R_6O-CO-C_{1-4}$ -alkyl groups or by an R_6O-CO group and
an $R_6O-CO-C_{1-4}$ -alkyl group wherein R_6 is as hereinbefore defined,

35 a pyrrolidinyl, piperidinyl or hexahydroazepinyl group substi-
tuted in the 1 position by the group R_{10} , whilst the above-
mentioned 5 to 7-membered rings are in each case additionally
substituted at a carbon atom by an R_6O-CO , $(R_7O-PO-OR_8)$,
40 $(R_7O-PO-R_9)$, $R_6O-CO-C_{1-4}$ -alkyl, bis- $(R_6O-CO)-C_{1-4}$ -alkyl,
 $(R_7O-PO-OR_8)-C_{1-4}$ -alkyl or $(R_7O-PO-R_9)-C_{1-4}$ -alkyl group wherein R_6
to R_{10} are as hereinbefore defined,

45 a pyrrolidinyl, piperidinyl or hexahydroazepinyl group substi-
tuted in the 1 position by the group R_{10} , whilst the above-
mentioned 5 to 7-membered rings in each case are additionally
substituted at carbon atoms by two R_6O-CO or $R_6O-CO-C_{1-4}$ -alkyl
50 groups or by an R_6O-CO group and an $R_6O-CO-C_{1-4}$ -alkyl group
wherein R_6 and R_{10} are as hereinbefore defined,

5

10

a pyrrolidinyl, piperidinyl or hexahydroazepinyl group substituted in the 1 position by an $R_6O-CO-C_{1-4}$ -alkyl, bis- $(R_6O-CO)-C_{1-4}$ -alkyl, $(R_6O-PO-OR_6)-C_{1-4}$ -alkyl or $(R_6O-PO-R_6)-C_{1-4}$ -alkyl group wherein R_6 to R_9 are as hereinbefore defined,

15

20

a pyrrolidinyl, piperidinyl or hexahydroazepinyl group substituted in the 1 position by an $R_6O-CO-C_{1-4}$ -alkyl, bis- $(R_6O-CO)-C_{1-4}$ -alkyl, $(R_6O-PO-OR_6)-C_{1-4}$ -alkyl or $(R_6O-PO-R_6)-C_{1-4}$ -alkyl group, whilst the abovementioned 5- to 7-membered rings in each case are additionally substituted at carbon atoms by one or two R_6O-CO or $R_6O-CO-C_{1-4}$ -alkyl groups or by an R_6O-CO group and an $R_6O-CO-C_{1-4}$ -alkyl group wherein R_6 to R_9 are as hereinbefore defined,

25

a 2-oxo-morpholino group which may be substituted by 1 to 4 C_{1-2} -alkyl groups,

30

35

a 2-oxo-morpholinyl group which is substituted in the 4 position by a hydrogen atom, by a C_{1-4} -alkyl, $R_6O-CO-C_{1-4}$ -alkyl, $(R_6O-PO-OR_6)-C_{1-4}$ -alkyl or $(R_6O-PO-R_6)-C_{1-4}$ -alkyl group, whilst R_6 to R_9 are as hereinbefore defined and the abovementioned 2-oxo-morpholinyl groups in each case are linked to a carbon atom of the group A,

40

an $R_{11}NR_9$ group wherein R_9 is as hereinbefore defined and

45

R_{11} denotes a 2-oxo-tetrahydrofuran-3-yl, 2-oxo-tetrahydrofuran-4-yl, 2-oxo-tetrahydropyran-3-yl, 2-oxo-tetrahydropyran-4-yl or 2-oxo-tetrahydropyran-5-yl group optionally substituted by one or two methyl groups,

50

or A and B together denotes a hydrogen, fluorine or chlorine atom,

55

a C_{1-6} -alkoxy group,

5 a C₂₋₆-alkoxy group which is substituted from position 2 onwards
by a hydroxy, C₁₋₄-alkoxy, amino, C₁₋₄-alkylamino, di-(C₁₋₄-al-
10 kyl)-amino, pyrrolidino, piperidino, hexahydroazepino, morpho-
lino, homomorpholino, piperazino, 4-(C₁₋₄-alkyl)-piperazino,
homopiperazino, 4-(C₁₋₄-alkyl)-homopiperazino or 1-imidazolyl
group,

15 a C₁₋₄-alkoxy group which is substituted by a pyrrolidinyl,
piperidinyl or hexahydroazepinyl group substituted in the 1
position by the group R₁₀, whilst R₁₀ is as hereinbefore de-
20 fined,

a C₁₋₆-alkoxy group which is substituted by an R₆O-CO,
(R₇O-PO-OR₈) or (R₇O-PO-R₈) group, whilst R₆ to R₈ are as
25 hereinbefore defined,

a C₃₋₇-cycloalkoxy or C₃₋₇-cycloalkyl-C₁₋₄-alkoxy group,

30 an amino, C₁₋₄-alkylamino, di-(C₁₋₄-alkyl)-amino, pyrrolidino,
piperidino, hexahydroazepino, morpholino, homomorpholino,
piperazino, 4-(C₁₋₄-alkyl)-piperazino, homopiperazino or
4-(C₁₋₄-alkyl)-homopiperazino group,

35 a 2-oxo-morpholino group which may be substituted by 1 or 2
methyl groups,

40 C denotes an -O-C₁₋₆-alkylene, -O-C₄₋₇-cycloalkylene, -O-C₁₋₃-al-
kylene-C₃₋₇-cycloalkylene, -O-C₄₋₇-cycloalkylene-C₁₋₃-alkylene or
-O-C₁₋₃-alkylene-C₃₋₇-cycloalkylene-C₁₋₃-alkylene group, whilst
the oxygen atom of the abovementioned group in each case is
45 linked to the bicyclic heteroaromatic ring,

50 an -O-C₁₋₆-alkylene group which is substituted by an R₆O-CO or
R₆O-CO-C₁₋₄-alkyl group, whilst R₆ is as hereinbefore defined and
the oxygen atom of the abovementioned-O-C₁₋₆-alkylene groups in
each case is linked to the bicyclic heteroaromatic ring,

an -O-C₂₋₆-alkylene group which is substituted from position 2 by a hydroxy, C₁₋₄-alkoxy, amino, C₁₋₄-alkylamino, di-(C₁₋₄-alkyl)-amino, pyrrolidino, piperidino, morpholino, piperazino or 4-(C₁₋₄-alkyl)-piperazino group and the oxygen atom of the abovementioned-O-C₂₋₆-alkylene groups in each case is linked to the bicyclic heteroaromatic ring,

a -C₁₋₆-alkylene group,

an -NR₄-C₁₋₆-alkylene, -NR₄-C₃₋₇-cycloalkylene, -NR₄-C₁₋₃-alkylene-C₃₋₇-cycloalkylene, -NR₄-C₃₋₇-cycloalkylene-C₁₋₃-alkylene or -NR₄-C₁₋₃-alkylene-C₃₋₇-cycloalkylene-C₁₋₃-alkylene group, whilst the -NR₄- moiety of the abovementioned groups in each case is linked to the bicyclic heteroaromatic ring and R₄ is as hereinbefore defined,

an oxygen atom, which is linked to a carbon atom of the group D, or

a NR₄ group, where the latter is linked to a carbon atom of the group D and R₄ is as hereinbefore defined,

D denotes an R₆O-CO-alkylene-NR₅, (R₆O-PO-OR₆)-alkylene-NR₅ or (R₆O-PO-R₆)-alkylene-NR₅ group wherein in each case the alkylene moiety, which is straight-chained and contains 1 to 6 carbon atoms, may additionally be substituted by one or two C₁₋₂-alkyl groups or by an R₆O-CO or R₆O-CO-C₁₋₂-alkyl group, whilst R₆ to R₅ are as hereinbefore defined,

a 4- to 7-membered alkyleneimino group which is substituted by an R₆O-CO, (R₆O-PO-OR₆), (R₆O-PO-R₆), R₆O-CO-C₁₋₄-alkyl, bis-(R₆O-CO)-C₁₋₄-alkyl, (R₆O-PO-OR₆)-C₁₋₄-alkyl or (R₆O-PO-R₆)-C₁₋₄-alkyl group wherein R₆ to R₅ are as hereinbefore defined,

a 4- to 7-membered alkyleneimino group which is substituted by two R₆O-CO or R₆O-CO-C₁₋₄-alkyl groups or by an R₆OCO group and an R₆O-CO-C₁₋₄-alkyl group wherein R₆ is as hereinbefore defined,

5

10

15

a piperazino or homopiperazino group which is substituted in the 4 position by the group R_{10} and additionally at a cyclic carbon atom by an R_6O-CO , $(R_7O-PO-OR_8)$, $(R_7O-PO-R_9)$, $R_6O-CO-C_{1-4}$ -alkyl, bis- $(R_6O-CO)-C_{1-4}$ -alkyl, $(R_7O-PO-OR_8)-C_{1-4}$ -alkyl or $(R_7O-PO-R_9)-C_{1-4}$ -alkyl group wherein R_6 to R_{10} are as hereinbefore defined,

20

a piperazino or homopiperazino group which is substituted in the 4 position by the group R_{10} and is additionally substituted at cyclic carbon atoms by two R_6O-CO or $R_6O-CO-C_{1-4}$ -alkyl groups or by an R_6O-CO group and an $R_6O-CO-C_{1-4}$ -alkyl group wherein R_6 and R_{10} are as hereinbefore defined,

25

a piperazino or homopiperazino group which is substituted in each case in the 4 position by an $R_6O-CO-C_{1-4}$ -alkyl, bis- $(R_6O-CO)-C_{1-4}$ -alkyl, $(R_7O-PO-OR_8)-C_{1-4}$ -alkyl or $(R_7O-PO-R_9)-C_{1-4}$ -alkyl group wherein R_6 to R_9 are as hereinbefore defined,

30

35

a piperazino or homopiperazino group which is substituted in the 4 position by an $R_6O-CO-C_{1-4}$ -alkyl, bis- $(R_6O-CO)-C_{1-4}$ -alkyl, $(R_7O-PO-OR_8)-C_{1-4}$ -alkyl or $(R_7O-PO-R_9)-C_{1-4}$ -alkyl group and is additionally substituted at cyclic carbon atoms by one or two R_6O-CO or $R_6O-CO-C_{1-4}$ -alkyl groups or by an R_6O-CO group and an $R_6O-CO-C_{1-4}$ -alkyl group wherein R_6 to R_9 are as hereinbefore defined,

40

45

a morpholino or homomorpholino group which is substituted in each case by an R_6O-CO , $(R_7O-PO-OR_8)$, $(R_7O-PO-R_9)$, $R_6O-CO-C_{1-4}$ -alkyl, bis- $(R_6O-CO)-C_{1-4}$ -alkyl, $(R_7O-PO-OR_8)-C_{1-4}$ -alkyl or $(R_7O-PO-R_9)-C_{1-4}$ -alkyl group wherein R_6 to R_9 are as hereinbefore defined,

50

a morpholino or homomorpholino group which is substituted by two R_6O-CO or $R_6O-CO-C_{1-4}$ -alkyl groups or by an R_6O-CO group and an $R_6O-CO-C_{1-4}$ -alkyl group wherein R_6 is as hereinbefore defined,

55

5 a pyrrolidinyl, piperidinyl or hexahydroazepinyl group substituted in the 1 position by the group R_{10} , whilst the abovementioned 5- to 7-membered rings in each case are additionally
10 substituted at a carbon atom by an R_6O-CO , $(R_7O-PO-OR_8)$, $(R_7O-PO-R_9)$, $R_6O-CO-C_{1-4}$ -alkyl, bis- $(R_6O-CO)-C_{1-4}$ -alkyl, $(R_7O-PO-OR_8)-C_{1-4}$ -alkyl or $(R_7O-PO-R_9)-C_{1-4}$ -alkyl group wherein R_6 to R_{10} are as hereinbefore defined,

15 a pyrrolidinyl, piperidinyl or hexahydroazepinyl group substituted in the 1 position by the group R_{10} , whilst the abovementioned 5- to 7-membered rings are in each case additionally
20 substituted at carbon atoms by two R_6O-CO or $R_6O-CO-C_{1-4}$ -alkyl groups or by an R_6O-CO group and an $R_6O-CO-C_{1-4}$ -alkyl group wherein R_6 and R_{10} are as hereinbefore defined,

25 a pyrrolidinyl, piperidinyl or hexahydroazepinyl group substituted in the 1 position by an $R_6O-CO-C_{1-4}$ -alkyl, bis- $(R_6O-CO)-C_{1-4}$ -alkyl, $(R_7O-PO-OR_8)-C_{1-4}$ -alkyl or $(R_7O-PO-R_9)-C_{1-4}$ -alkyl group wherein R_6 to R_9 are as hereinbefore defined,

30 a pyrrolidinyl, piperidinyl or hexahydroazepinyl group substituted in the 1 position by an $R_6O-CO-C_{1-4}$ -alkyl, bis- $(R_6O-CO)-C_{1-4}$ -alkyl, $(R_7O-PO-OR_8)-C_{1-4}$ -alkyl or $(R_7O-PO-R_9)-C_{1-4}$ -alkyl group, whilst the abovementioned 5- to 7-membered rings are in each
35 case additionally substituted at carbon atoms by one or two R_6O-CO or $R_6O-CO-C_{1-4}$ -alkyl groups or by an R_6O-CO group and an $R_6O-CO-C_{1-4}$ -alkyl group wherein R_6 to R_9 are as hereinbefore defined,
40

45 a 2-oxo-morpholino group which may be substituted by 1 to 4 C_{1-2} -alkyl groups,

50 a 2-oxo-morpholinyl group which is substituted in the 4 position by a hydrogen atom, by a C_{1-4} -alkyl, $R_6O-CO-C_{1-4}$ -alkyl, $(R_7O-PO-OR_8)-C_{1-4}$ -alkyl or $(R_7O-PO-R_9)-C_{1-4}$ -alkyl group, whilst R_6 to R_9 are as hereinbefore defined and the abovementioned 2-oxo-

5 morpholinyl groups are in each case linked to a carbon atom of the group C,

10 an $R_{11}NR_5$ group wherein R_5 and R_{11} are as hereinbefore defined, or

15 C and D together denote a hydrogen, fluorine or chlorine atom,

a C_{1-6} -alkoxy group,

20 a C_{2-6} -alkoxy group which is substituted from position 2 by a hydroxy, C_{1-4} -alkoxy, amino, C_{1-4} -alkylamino, di-(C_{1-4} -alkyl)-amino, pyrrolidino, piperidino, hexahydroazepino, morpholino, homomorpholino, piperazino, 4-(C_{1-4} -alkyl)-piperazino, homopiperazino, 4-(C_{1-4} -alkyl)-homopiperazino or 1-imidazolyl group,

25 a C_{1-4} -alkoxy group which is substituted by a pyrrolidinyl, piperidinyl or hexahydroazepinyl group substituted in the 1 position by the group R_{10} , whilst R_{10} is as hereinbefore defined,

30 a C_{1-6} -alkoxy group which is substituted by an R_6O-CO , ($R_6O-PO-OR_9$) or ($R_7O-PO-R_9$) group, whilst R_6 to R_9 are as hereinbefore defined,

35 a C_{3-7} -cycloalkoxy or C_{3-7} -cycloalkyl- C_{1-4} -alkoxy group

40 an amino, C_{1-4} -alkylamino, di-(C_{1-4} -alkyl)-amino, pyrrolidino, piperidino, hexahydroazepino, morpholino, homomorpholino, piperazino, 4-(C_{1-4} -alkyl)-piperazino, homopiperazino or 4-(C_{1-4} -alkyl)-homopiperazino group,

45 a 2-oxo-morpholino group which may be substituted by 1 or 2 methyl groups,

50 with the proviso that at least one of the groups B or D or A together with B or C together with D contains an optionally

5 substituted 2-oxo-morpholinyl group, an (R₇O-PO-OR₈) or (R₇O-PO-R₉) group, or

10 that at least one of the groups B or D contains an optionally substituted 2-oxo-tetrahydrofuran-3-yl, 2-oxo-tetrahydrofuran-4-yl, 2-oxo-tetrahydropyran-3-yl, 2-oxo-tetrahydropyran-4-yl or 2-oxo-tetrahydropyran-5-yl group, or

15 that at least one of the groups A, B, C or D or A together with B or C together with D contains an R₆O-CO group and additionally one of the groups A, B, C or D or A together with B or C together with D contains a primary, secondary or tertiary amino function, whilst the nitrogen atom of this amino function is not linked to a carbon atom of an aromatic group.

25 By the aryl moieties mentioned in the definition of the above-mentioned groups is meant a phenyl group which may in each case be monosubstituted by R₁₂, mono-, di- or trisubstituted by R₁₁, or monosubstituted by R₁₂ and additionally mono- or disubstituted by R₁₁, whilst the substituents may be identical or different and

35 R₁₂ denotes a cyano, carboxy, C₁₋₄-alkoxycarbonyl, aminocarbonyl, C₁₋₄-alkylaminocarbonyl, di-(C₁₋₄-alkyl)-aminocarbonyl, C₁₋₄-alkylsulphenyl, C₁₋₄-alkylsulphinyl, C₁₋₄-alkylsulphonyl, hydroxy, C₁₋₄-alkylsulphonyloxy, trifluoromethyloxy, nitro, amino, C₁₋₄-alkylamino, di-(C₁₋₄-alkyl)-amino, C₁₋₄-alkyl-carbonylamino, N-(C₁₋₄-alkyl)-C₁₋₄-alkylcarbonylamino, C₁₋₄-alkylsulphonylamino, N-(C₁₋₄-alkyl)-C₁₋₄-alkylsulphonylamino, aminosulphonyl, C₁₋₄-alkylaminosulphonyl or di-(C₁₋₄-alkyl)-aminosulphonyl group or a carbonyl group which is substituted by a 5- to 7-membered alkyleneimino group, whilst in the 45 abovementioned 6- to 7-membered alkyleneimino groups in each case a methylene group in the 4 position may be replaced by an oxygen or sulphur atom, by a sulphinyl, sulphonyl, imino or N-(C₁₋₄-alkyl)-imino group, and

R_{13} denotes a fluorine, chlorine, bromine or iodine atom, a C_{1-4} -alkyl, trifluoromethyl or C_{1-4} -alkoxy group or

two groups R_{13} , if they are bound to adjacent carbon atoms, together denote a C_{3-5} -alkylene, methylenedioxy or 1,3-butadien-1,4-ylene group,

whilst of the abovementioned compounds the preferred ones are those wherein

R_a to R_d , A and X are as hereinbefore defined,

B denotes an R_6O-CO -alkylene- NR_5 , $(R_7O-PO-OR_8)$ -alkylene- NR_5 or $(R_7O-PO-R_9)$ -alkylene- NR_5 group wherein in each case the alkylene moiety, which is straight-chained and contains 1 to 6 carbon atoms, may additionally be substituted by one or two C_{1-2} -alkyl groups or by an R_6O-CO or $R_6O-CO-C_{1-2}$ -alkyl group,

a 4- to 7-membered alkyleneimino group which is substituted by an R_6O-CO , $(R_7O-PO-OR_8)$, $(R_7O-PO-R_9)$, $R_6O-CO-C_{1-4}$ -alkyl, bis- $(R_6O-CO)-C_{1-4}$ -alkyl, $(R_7O-PO-OR_8)-C_{1-4}$ -alkyl or $(R_7O-PO-R_9)-C_{1-4}$ -alkyl group,

a piperazino or homopiperazino group which is substituted in the 4 position by the group R_{10} and additionally at a cyclic carbon atom by an R_6O-CO , $(R_7O-PO-OR_8)$, $(R_7O-PO-R_9)$, $R_6O-CO-C_{1-4}$ -alkyl, bis- $(R_6O-CO)-C_{1-4}$ -alkyl, $(R_7O-PO-OR_8)-C_{1-4}$ -alkyl or $(R_7O-PO-R_9)-C_{1-4}$ -alkyl group,

a piperazino or homopiperazino group which in each case is substituted in the 4 position by an $R_6O-CO-C_{1-4}$ -alkyl, bis- $(R_6O-CO)-C_{1-4}$ -alkyl, $(R_7O-PO-OR_8)-C_{1-4}$ -alkyl or $(R_7O-PO-R_9)-C_{1-4}$ -alkyl group,

a pyrrolidinyl, piperidinyl or hexahydroazepinyl group substituted in the 1 position by the group R_{10} , whilst the abovementioned 5- to 7-membered rings in each case are additionally

substituted at a carbon atom by an R_6O-CO , $(R_7O-PO-OR_8)$, $(R_7O-PO-R_9)$, $R_6O-CO-C_{1-4}$ -alkyl, bis- $(R_6O-CO)-C_{1-4}$ -alkyl, $(R_7O-PO-OR_8)-C_{1-4}$ -alkyl or $(R_7O-PO-R_9)-C_{1-4}$ -alkyl group,

a pyrrolidinyl, piperidinyl or hexahydroazepinyl group substituted in the 1 position by an $R_6O-CO-C_{1-4}$ -alkyl, bis- $(R_6O-CO)-C_{1-4}$ -alkyl, $(R_7O-PO-OR_8)-C_{1-4}$ -alkyl or $(R_7O-PO-R_9)-C_{1-4}$ -alkyl group,

a 2-oxo-morpholino group which may be substituted by 1 or 2 methyl groups,

a 2-oxo-morpholinyl group which is substituted in the 4 position by a hydrogen atom, by a C_{1-4} -alkyl, $R_6O-CO-C_{1-4}$ -alkyl, $(R_7O-PO-OR_8)-C_{1-4}$ -alkyl or $(R_7O-PO-R_9)-C_{1-4}$ -alkyl group, whilst R_6 to R_9 are as hereinbefore defined and the abovementioned 2-oxo-morpholinyl groups in each case are linked to a carbon atom of the group A, or

A and B together denote a hydrogen, fluorine or chlorine atom,

a C_{1-6} -alkoxy group,

a C_{2-6} -alkoxy group which is substituted from position 2 by a hydroxy, C_{1-4} -alkoxy, amino, C_{1-4} -alkylamino, di- $(C_{1-4}$ -alkyl)-amino, pyrrolidino, piperidino, hexahydroazepino, morpholino, homomorpholino, piperazino, 4- $(C_{1-4}$ -alkyl)-piperazino, homopiperazino or 4- $(C_{1-4}$ -alkyl)-homopiperazino group,

a C_{1-6} -alkoxy group which is substituted by an R_6O-CO , $(R_7O-PO-OR_8)$ or $(R_7O-PO-R_9)$ group,

a C_{4-7} -cycloalkoxy or C_{3-7} -cycloalkyl- C_{1-4} -alkoxy group,

an amino, C_{1-4} -alkylamino, di- $(C_{1-4}$ -alkyl)-amino, pyrrolidino, piperidino, hexahydroazepino, morpholino, homomorpholino, piperazino, 4- $(C_{1-4}$ -alkyl)-piperazino, homopiperazino or 4- $(C_{1-4}$ -alkyl)-homopiperazino group,

5
10 a 2-oxo-morpholino group which may be substituted by 1 or 2 methyl groups,

15 C denotes an -O-C₁₋₆-alkylene, -O-C₄₋₇-cycloalkylene, -O-C₁₋₃-alkylene-C₃₋₇-cycloalkylene, -O-C₄₋₇-cycloalkylene-C₁₋₃-alkylene or -O-C₁₋₃-alkylene-C₃₋₇-cycloalkylene-C₁₋₃-alkylene group, whilst the oxygen atom of the abovementioned group in each case is linked to the bicyclic heteroaromatic ring,

20 an -O-C₁₋₆-alkylene group which is substituted by an R₆O-CO or R₆O-CO-C₁₋₄-alkyl group, whilst R₆ is as hereinbefore defined,

25 an -O-C₂₋₆-alkylene group which is substituted from position 2 onwards by a hydroxy, C₁₋₄-alkoxy, amino, C₁₋₄-alkylamino, di-(C₁₋₄-alkyl)-amino, pyrrolidino, piperidino, morpholino, piperazino or 4-(C₁₋₄-alkyl)-piperazino group,

30 a -C₁₋₆-alkylene group,

35 an -NR₄-C₁₋₆-alkylene, -NR₄-C₃₋₇-cycloalkylene, -NR₄-C₁₋₃-alkylene-C₃₋₇-cycloalkylene, -NR₄-C₃₋₇-cycloalkylene-C₁₋₃-alkylene or -NR₄-C₁₋₃-alkylene-C₃₋₇-cycloalkylene-C₁₋₃-alkylene group, whilst the -NR₄- moiety of the abovementioned groups in each case is linked to the bicyclic heteroaromatic ring,

40 an oxygen atom, which is linked to a carbon atom of the group D, or

45 a NR₄ group, this being linked to a carbon atom of the group D, and

50 D denotes an R₆O-CO-alkylene-NR₅, (R₆O-PO-OR₆)-alkylene-NR₅ or (R₆O-PO-R₆)-alkylene-NR₅ group wherein in each case the alkylene moiety, which is straight-chained and contains 1 to 6 carbon atoms, may additionally be substituted by one or two C₁₋₂-alkyl groups or by an R₆O-CO or R₆O-CO-C₁₋₂-alkyl group,

5

10

a 4- to 7-membered alkyleneimino group which is substituted by an R_6O-CO , $(R_7O-PO-OR_8)$, $(R_7O-PO-R_9)$, $R_6O-CO-C_{1-4}$ -alkyl, bis- $(R_6O-CO)-C_{1-4}$ -alkyl, $(R_7O-PO-OR_8)-C_{1-4}$ -alkyl or $(R_7O-PO-R_9)-C_{1-4}$ -alkyl group,

15

a piperazino or homopiperazino group which is substituted in the 4 position by the group R_{10} and additionally at a cyclic carbon atom by an R_6O-CO , $(R_7O-PO-OR_8)$, $(R_7O-PO-R_9)$, $R_6O-CO-C_{1-4}$ -alkyl, bis- $(R_6O-CO)-C_{1-4}$ -alkyl, $(R_7O-PO-OR_8)-C_{1-4}$ -alkyl or $(R_7O-PO-R_9)-C_{1-4}$ -alkyl group,

20

25

a piperazino or homopiperazino group which is substituted in each case in the 4 position by an $R_6O-CO-C_{1-4}$ -alkyl, bis- $(R_6O-CO)-C_{1-4}$ -alkyl, $(R_7O-PO-OR_8)-C_{1-4}$ -alkyl or $(R_7O-PO-R_9)-C_{1-4}$ -alkyl group,

30

a pyrrolidinyl, piperidinyl or hexahydroazepinyl group substituted in the 1 position by the group R_{10} , whilst the abovementioned 5- to 7-membered rings in each case are additionally substituted at a carbon atom by an R_6O-CO , $(R_7O-PO-OR_8)$, $(R_7O-PO-R_9)$, $R_6O-CO-C_{1-4}$ -alkyl, bis- $(R_6O-CO)-C_{1-4}$ -alkyl, $(R_7O-PO-OR_8)-C_{1-4}$ -alkyl or $(R_7O-PO-R_9)-C_{1-4}$ -alkyl group,

35

40

a pyrrolidinyl, piperidinyl or hexahydroazepinyl group substituted in the 1 position by an $R_6O-CO-C_{1-4}$ -alkyl, bis- $(R_6O-CO)-C_{1-4}$ -alkyl, $(R_7O-PO-OR_8)-C_{1-4}$ -alkyl or $(R_7O-PO-R_9)-C_{1-4}$ -alkyl group,

45

a 2-oxo-morpholino group which may be substituted by 1 or 2 methyl groups,

50

a 2-oxo-morpholinyl group which is substituted in the 4 position by a hydrogen atom, by a C_{1-4} -alkyl, $R_6O-CO-C_{1-4}$ -alkyl, $(R_7O-PO-OR_8)-C_{1-4}$ -alkyl or $(R_7O-PO-R_9)-C_{1-4}$ -alkyl group, whilst R_6 to R_9 are as hereinbefore defined and the abovementioned 2-oxo-

55

morpholinyl groups are in each case linked to a carbon atom of the group C, or

C and D together denote a hydrogen, fluorine or chlorine atom,

a C₁₋₆-alkoxy group,

a C₂₋₆-alkoxy group which is substituted from position 2 by a hydroxy, C₁₋₄-alkoxy, amino, C₁₋₄-alkylamino, di-(C₁₋₄-alkyl)-amino, pyrrolidino, piperidino, hexahydroazepino, morpholino, homomorpholino, piperazino, 4-(C₁₋₄-alkyl)-piperazino, homopiperazino or 4-(C₁₋₄-alkyl)-homopiperazino group,

a C₁₋₆-alkoxy group which is substituted by an R₆O-CO, (R₆O-PO-OR₈) or (R₇O-PO-R₉) group,

a C₄₋₇-cycloalkoxy or C₃₋₇-cycloalkyl-C₁₋₄-alkoxy group

an amino, C₁₋₄-alkylamino, di-(C₁₋₄-alkyl)-amino, pyrrolidino, piperidino, hexahydroazepino, morpholino, homomorpholino, piperazino, 4-(C₁₋₄-alkyl)-piperazino, homopiperazino or 4-(C₁₋₄-alkyl)-homopiperazino group,

a 2-oxo-morpholino group which may be substituted by 1 or 2 methyl groups,

with the proviso that at least one of the groups B or D or A together with B or C together with D contains an optionally substituted 2-oxo-morpholinyl group, a (R₇O-PO-OR₈) or (R₇O-PO-R₉) group, or

that at least one of the groups A, B, C or D or A together with B or C together with D contains an R₆O-CO group and additionally one of the groups A, B, C or D or A together with B or C together with D contains a primary, secondary or tertiary amino function, whilst the nitrogen atom of this amino function is not linked to a carbon atom of an aromatic group,

whilst in the abovementioned groups A to D R_1 to R_{10} are as hereinbefore defined,

particularly those compounds wherein

R_a denotes a hydrogen atom,

R_b denotes a phenyl, benzyl or 1-phenylethyl group wherein the phenyl nucleus is substituted in each case by the groups R_1 to R_3 , whilst

R_1 and R_2 , which may be identical or different, each denote a hydrogen, fluorine, chlorine, bromine or iodine atom,

a methyl, ethyl, hydroxy, methoxy, ethoxy, amino, cyano, vinyl or ethynyl group,

an aryl, aryloxy, arylmethyl or arylmethoxy group,

a methyl or methoxy group substituted by 1 to 3 fluorine atoms or

R_1 together with R_2 , if they are bound to adjacent carbon atoms, denote a $-\text{CH}=\text{CH}-\text{CH}=\text{CH}-$, $-\text{CH}=\text{CH}-\text{NH}$ or $-\text{CH}=\text{N}-\text{NH}$ group and

R_3 denotes a hydrogen, fluorine, chlorine or bromine atom,

R_c and R_d in each case denote a hydrogen atom,

X denotes a nitrogen atom,

A denotes an $-\text{O}-\text{C}_{1,4}-$ alkylene, $-\text{O}-\text{C}_{4,7}-$ cycloalkylene, $-\text{O}-\text{C}_{1,3}-$ alkylene- $\text{C}_{3,7}-$ cycloalkylene, $-\text{O}-\text{C}_{4,7}-$ cycloalkylene- $\text{C}_{1,3}-$ alkylene or $-\text{O}-\text{C}_{1,3}-$ alkylene- $\text{C}_{3,7}-$ cycloalkylene- $\text{C}_{1,3}-$ alkylene group, whilst

the oxygen atom of the abovementioned groups in each case is linked to the bicyclic heteroaromatic ring,

an -O-C₂₋₄-alkylene group which is substituted from position 2 onwards by a hydroxy group, whilst the oxygen atom of the abovementioned-O-C₂₋₄-alkylene groups in each case is linked to the bicyclic heteroaromatic ring, or

an oxygen atom, this being linked to a carbon atom of the group B,

B denotes an R₆O-CO-alkylene-NR₅, (R₆O-PO-OR₆)-alkylene-NR₅ or (R₆O-PO-R₆)-alkylene-NR₅ group wherein in each case the alkylene moiety, which is straight-chained and contains 1 to 4 carbon atoms, may additionally be substituted by one or two C₁₋₂-alkyl groups or by an R₆O-CO or R₆O-CO-C₁₋₂-alkyl group, whilst

R₅ denotes a hydrogen atom,

a C₁₋₄-alkyl group which may be substituted by an R₆O-CO group,

a C₂₋₄-alkyl group which is substituted from position 2 by a hydroxy or C₁₋₄-alkoxy group,

a C₃₋₆-cycloalkyl or C₁₋₆-cycloalkyl-C₁₋₃-alkyl group,

R₆, R₇ and R₈, which may be identical or different, in each case denote a hydrogen atom,

a C₁₋₆-alkyl group which may be substituted from position 2 onwards by a hydroxy, C₁₋₄-alkoxy or di-(C₁₋₄-alkyl)-amino group or by a 4- to 7-membered alkyleneimino group, whilst in the abovementioned 6- to 7-membered alkyleneimino groups in each case a methylene group in the 4 position may be replaced by an oxygen atom or by an N-(C₁₋₂-alkyl)-imino group,

5 a C₄₋₆-cycloalkyl group,

10 a C₃₋₅-alkenyl or C₃₋₅-alkynyl group, whilst the unsaturated moiety may not be linked to the oxygen atom,

15 a C₃₋₆-cycloalkyl-C₁₋₄-alkyl, aryl, aryl-C₁₋₄-alkyl or R₆CO-O-(R₆CR₆) group, whilst

20 R₆ and R₆, which may be identical or different, in each case denote a hydrogen atom or a C₁₋₄-alkyl group and

R₆ denotes a C₁₋₄-alkyl, C₃₋₆-cycloalkyl, C₁₋₄-alkoxy or C₃₋₆-cycloalkoxy group,

25 and R₆ denotes a C₁₋₄-alkyl group,

30 a 4- to 7-membered alkyleneimino group which is substituted by an R₆O-CO, R₆O-CO-C₁₋₄-alkyl or bis-(R₆O-CO)-C₁₋₄-alkyl group wherein R₆ is as hereinbefore defined,

35 a 4- to 7-membered alkyleneimino group which is substituted by two R₆O-CO or R₆O-CO-C₁₋₄-alkyl groups wherein R₆ is as hereinbefore defined,

40 a piperazino or homopiperazino group which is substituted in the 4 position by the group R₁₀ and additionally at a cyclic carbon atom by an R₆O-CO, R₆O-CO-C₁₋₄-alkyl or bis-(R₆O-CO)-C₁₋₄-alkyl group wherein R₆ is as hereinbefore defined and

45 R₁₀ denotes a hydrogen atom, a methyl or ethyl group,

50 a piperazino or homopiperazino group which is substituted in the 4 position by the group R₁₀ and is additionally substituted at cyclic carbon atoms by two R₆O-CO or R₆O-CO-C₁₋₄-alkyl groups wherein R₆ and R₁₀ are as hereinbefore defined,

5
10 a piperazino or homopiperazino group which in each case is substituted in the 4 position by an $R_6O-CO-C_{1,4}$ -alkyl, bis- $(R_6O-CO)-C_{1,4}$ -alkyl, $(R_6O-PO-OR_6)-C_{1,4}$ -alkyl or $(R_6O-PO-R_6)-C_{1,4}$ -alkyl group wherein R_6 to R_8 are as hereinbefore defined,

15 a piperazino or homopiperazino group which is substituted in the 4 position by an $R_6O-CO-C_{1,4}$ -alkyl or bis- $(R_6O-CO)-C_{1,4}$ -alkyl group and is additionally substituted at cyclic carbon atoms by one or two R_6O-CO or $R_6O-CO-C_{1,4}$ -alkyl groups wherein R_6 is as hereinbefore defined,

20 a morpholino or homomorpholino group which is substituted in each case by an R_6O-CO , $R_6O-CO-C_{1,4}$ -alkyl, or bis- $(R_6O-CO)-C_{1,4}$ -alkyl group wherein R_6 is as hereinbefore defined,

25 a morpholino or homomorpholino group which is substituted by two R_6O-CO or $R_6O-CO-C_{1,4}$ -alkyl groups wherein R_6 is as hereinbefore defined,

30 a pyrrolidinyl, piperidinyl or hexahydroazepinyl group substituted in the 1 position by the group R_{10} , whilst the above-mentioned 5- to 7-membered rings in each case are additionally substituted at a carbon atom by an R_6O-CO , $R_6O-CO-C_{1,4}$ -alkyl or bis- $(R_6O-CO)-C_{1,4}$ -alkyl group wherein R_6 and R_{10} are as hereinbefore defined,

35
40 a pyrrolidinyl, piperidinyl or hexahydroazepinyl group substituted in the 1 position by the group R_{10} , whilst the above-mentioned 5- to 7-membered rings are in each case additionally substituted at carbon atoms by two R_6O-CO or $R_6O-CO-C_{1,4}$ -alkyl groups wherein R_6 and R_{10} are as hereinbefore defined,

45
50 a pyrrolidinyl, piperidinyl or hexahydroazepinyl group substituted in the 1 position by an $R_6O-CO-C_{1,4}$ -alkyl, bis- $(R_6O-CO)-C_{1,4}$ -alkyl, $(R_6O-PO-OR_6)-C_{1,4}$ -alkyl or $(R_6O-PO-R_6)-C_{1,4}$ -alkyl group wherein R_6 to R_8 are as hereinbefore defined,

5 a pyrrolidinyl, piperidinyl or hexahydroazepinyl group substituted in the 1 position by an $R_6O-CO-C_{1-4}$ -alkyl or bis-
10 $(R_6O-CO)-C_{1-4}$ -alkyl group, whilst the abovementioned 5- to 7-membered rings are in each case additionally substituted at carbon atoms by one or two R_6O-CO or $R_6O-CO-C_{1-4}$ -alkyl groups wherein R_6 is as hereinbefore defined,

15 a 2-oxo-morpholino group which may be substituted by 1 to 4 C_{1-2} -alkyl groups,

20 a 2-oxo-morpholinyl group which is substituted in the 4 position by a hydrogen atom, by a C_{1-4} -alkyl or $R_6O-CO-C_{1-4}$ -alkyl group, whilst R_6 is as hereinbefore defined and the abovementioned 2-oxo-morpholinyl groups in each case are linked to a
25 carbon atom of the group A,

an $R_{11}NR_5$ group wherein R_5 is as hereinbefore defined and

30 R_{11} denotes a 2-oxo-tetrahydrofuran-3-yl, 2-oxo-tetrahydrofuran-4-yl, 2-oxo-tetrahydropyran-3-yl, 2-oxo-tetrahydropyran-4-yl or 2-oxo-tetrahydropyran-5-yl group optionally substituted by one or two methyl groups,

35 or A and B together denote a hydrogen atom,

a C_{1-4} -alkoxy group,

40 a C_{1-4} -alkoxy group which is substituted from position 2 by a hydroxy, C_{1-4} -alkoxy, amino, C_{1-4} -alkylamino, di- $(C_{1-4}$ -alkyl)-amino, pyrrolidino, piperidino, morpholino, piperazino or 4- $(C_{1-4}$ -alkyl)-piperazino group,

45 a C_{1-4} -alkoxy group which is substituted by a pyrrolidinyl or piperidinyl group substituted in the 1 position by the group R_{10} , whilst R_{10} is as hereinbefore defined,
50

5 a C₁₋₄-alkoxy group which is substituted by an R₆O-CO group,
whilst R₆ is as hereinbefore defined,

10 a C₄₋₇-cycloalkoxy or C₃₋₇-cycloalkyl-C₁₋₄-alkoxy group,

15 C denotes an -O-C₁₋₄-alkylene, -O-C₄₋₇-cycloalkylene,
-O-C₁₋₃-alkylene-C₁₋₇-cycloalkylene, -O-C₄₋₇-cyclo-
alkylene-C₁₋₃-alkylene or -O-C₁₋₃-alkylene-C₃₋₇-cycloal-
kylene-C₁₋₃-alkylene group, whilst the oxygen atom of the
abovementioned group in each case is linked to the bicyclic
heteroaromatic ring,

20 an -O-C₂₋₄-alkylene group which is substituted from position 2
onwards by a hydroxy group, whilst the oxygen atom of the
abovementioned-O-C₂₋₄-alkylene groups in each case is linked to
25 the bicyclic heteroaromatic ring, or

30 an oxygen atom, which is linked to a carbon atom of the group
D,

35 D denotes an R₆O-CO-alkylene-NR₅, (R₆O-PO-OR₆)-alkylene-NR₅ or
(R₆O-PO-R₆)-alkylene-NR₅ group wherein in each case the alkylene
moiety, which is straight-chained and contains 1 to 4 carbon
atoms, may additionally be substituted by one or two C₁₋₂-alkyl
groups or by an R₆O-CO or R₆O-CO-C₁₋₂-alkyl group, whilst R₅ to
R₆ are as hereinbefore defined,

40 a 4- to 7-membered alkyleneimino group which is substituted by
an R₆O-CO, R₆O-CO-C₁₋₄-alkyl or bis-(R₆O-CO)-C₁₋₄-alkyl group
wherein R₆ is as hereinbefore defined,

45 a 4- to 7-membered alkyleneimino group which is substituted by
two R₆O-CO or R₆O-CO-C₁₋₄-alkyl groups wherein R₆ is as
hereinbefore defined,

50 a piperazino or homopiperazino group which is substituted in
the 4 position by the group R₁₀ and additionally at a cyclic

5 carbon atom by an R_6O-CO , $R_6O-CO-C_{1-4}$ -alkyl or bis- $(R_6O-CO)-C_{1-4}$ -alkyl group wherein R_6 and R_{10} are as hereinbefore defined,

10 a piperazino or homopiperazino group which is substituted in the 4 position by the group R_{10} and is additionally substituted at cyclic carbon atoms by two R_6O-CO or $R_6O-CO-C_{1-4}$ -alkyl groups wherein R_6 and R_{10} are as hereinbefore defined,

15 a piperazino or homopiperazino group which is substituted in each case in the 4 position by an $R_6O-CO-C_{1-4}$ -alkyl, bis- $(R_6O-CO)-C_{1-4}$ -alkyl, $(R_6O-PO-OR_6)-C_{1-4}$ -alkyl or $(R_6O-PO-R_6)-C_{1-4}$ -alkyl group wherein R_6 to R_9 are as hereinbefore defined,

20 a piperazino or homopiperazino group which is substituted in the 4 position by an $R_6O-CO-C_{1-4}$ -alkyl or bis- $(R_6O-CO)-C_{1-4}$ -alkyl group and is additionally substituted at cyclic carbon atoms by one or two R_6O-CO or $R_6O-CO-C_{1-4}$ -alkyl groups wherein R_6 is as hereinbefore defined,

25 a morpholino or homomorpholino group which is substituted in each case by an R_6O-CO , $R_6O-CO-C_{1-4}$ -alkyl, or bis- $(R_6O-CO)-C_{1-4}$ -alkyl group wherein R_6 is as hereinbefore defined,

30 a morpholino or homomorpholino group which is substituted in each case by an R_6O-CO , $R_6O-CO-C_{1-4}$ -alkyl, or bis- $(R_6O-CO)-C_{1-4}$ -alkyl group wherein R_6 is as hereinbefore defined,

35 a morpholino or homomorpholino group which is substituted in each case by an R_6O-CO , $R_6O-CO-C_{1-4}$ -alkyl, or bis- $(R_6O-CO)-C_{1-4}$ -alkyl group wherein R_6 is as hereinbefore defined,

40 a pyrrolidinyl, piperidinyl or hexahydroazepinyl group substituted in the 1 position by the group R_{10} , whilst the above-mentioned 5- to 7-membered rings in each case are additionally substituted at a carbon atom by an R_6O-CO , $R_6O-CO-C_{1-4}$ -alkyl or bis- $(R_6O-CO)-C_{1-4}$ -alkyl group wherein R_6 and R_{10} are as hereinbefore defined,

45 a pyrrolidinyl, piperidinyl or hexahydroazepinyl group substituted in the 1 position by the group R_{10} , whilst the above-mentioned 5- to 7-membered rings are in each case additionally

5

10

15

20

25

30

35

40

45

50

55

substituted at carbon atoms by two R_6O-CO or $R_6O-CO-C_{1-4}$ -alkyl groups wherein R_6 and R_{10} are as hereinbefore defined,

a pyrrolidinyl, piperidinyl or hexahydroazepinyl group substituted in the 1 position by an $R_6O-CO-C_{1-4}$ -alkyl, bis- $(R_6O-CO)-C_{1-4}$ -alkyl, $(R_7O-PO-OR_8)-C_{1-4}$ -alkyl or $(R_7O-PO-R_9)-C_{1-4}$ -alkyl group wherein R_6 to R_9 are as hereinbefore defined,

a pyrrolidinyl, piperidinyl or hexahydroazepinyl group substituted in the 1 position by an $R_6O-CO-C_{1-4}$ -alkyl or bis- $(R_6O-CO)-C_{1-4}$ -alkyl group, whilst the abovementioned 5- to 7-membered rings are in each case additionally substituted at carbon atoms by one or two R_6O-CO or $R_6O-CO-C_{1-4}$ -alkyl groups wherein R_6 is as hereinbefore defined,

a 2-oxo-morpholino group which may be substituted by 1 to 4 C_{1-2} -alkyl groups,

a 2-oxo-morpholinyl group which is substituted in the 4 position by a hydrogen atom, by a C_{1-4} -alkyl or $R_6O-CO-C_{1-4}$ -alkyl group, whilst R_6 is as hereinbefore defined and the abovementioned 2-oxo-morpholinyl groups are in each case linked to a carbon atom of the group C,

an $R_{11}NR_5$ group wherein R_5 and R_{11} are as hereinbefore defined, or

C and D together denote a hydrogen atom,

a C_{1-4} -alkoxy group,

a C_{2-4} -alkoxy group which is substituted from position 2 by a hydroxy, C_{1-4} -alkoxy, amino, C_{1-4} -alkylamino, di- $(C_{1-4}$ -alkyl)-amino, pyrrolidino, piperidino, morpholino, piperazino or 4- $(C_{1-4}$ -alkyl)-piperazino group,

5

10

a C₁₋₄-alkoxy group which is substituted by a pyrrolidinyl or piperidinyl group substituted in the 1 position by the group R₁₀, whilst R₁₀ is as hereinbefore defined,

15

a C₁₋₄-alkoxy group which is substituted by an R₆O-CO group, whilst R₆ is as hereinbefore defined,

20

a C₄₋₇-cycloalkoxy or C₃₋₇-cycloalkyl-C₁₋₄-alkoxy group

with the proviso that at least one of the groups B or D or A together with B or C together with D contains an optionally substituted 2-oxo-morpholinyl group, a (R₇O-PO-OR₈) or (R₇O-PO-R₉) group, or

25

that at least one of the groups B or D contains an optionally substituted 2-oxo-tetrahydrofuran-3-yl, 2-oxo-tetrahydrofuran-4-yl, 2-oxo-tetrahydropyran-3-yl, 2-oxo-tetrahydropyran-4-yl or 2-oxo-tetrahydropyran-5-yl group, or

30

that at least one of the groups A, B, C or D or A together with B or C together with D contains an R₆O-CO group and additionally one of the groups A, B, C or D or A together with B or C together with D contains a primary, secondary or tertiary amino function, whilst the nitrogen atom of this amino function is not linked to a carbon atom of an aromatic group,

35

40

whilst by the aryl moieties mentioned in the definition of the abovementioned groups is meant a phenyl group which in each case may be monosubstituted by R₁₂, mono- or disubstituted by R₁₃, or monosubstituted by R₁₂ and additionally mono- or disubstituted by R₁₃, whilst the substituents may be identical or different and

45

50

R₁₂ denotes a cyano, C₁₋₂-alkoxycarbonyl, aminocarbonyl, C₁₋₂-alkylaminocarbonyl, di-(C₁₋₂-alkyl)-aminocarbonyl, C₁₋₂-alkylsulphenyl, C₁₋₂-alkylsulphinyl, C₁₋₂-alkylsulphonyl,

55

hydroxy, nitro, amino, C₁₋₄-alkylamino or di-(C₁₋₄-alkyl)-amino group and

R₁₃ denotes a fluorine, chlorine, bromine or iodine atom, a C₁₋₂-alkyl, trifluoromethyl or C₁₋₂-alkoxy group or

two groups R₁₃, if they are bound to adjacent carbon atoms, together denote a C₃₋₅-alkylene, methylenedioxy or 1,3-butadien-1,4-ylene group,

the tautomers, stereoisomers and salts thereof.

Particularly preferred compounds of general formula I are those wherein

R_a denotes a hydrogen atom,

R_b denotes a phenyl, benzyl or 1-phenylethyl group wherein the phenyl nucleus is substituted in each case by the groups R₁ to R₃, whilst

R₁ and R₂, which may be identical or different, each denote a hydrogen, fluorine, chlorine or bromine atom,

a methyl, trifluoromethyl, methoxy, ethynyl or cyano group and

R₃ denotes a hydrogen atom,

R_c and R_d in each case denote a hydrogen atom,

X denotes a nitrogen atom,

A denotes an -O-C₁₋₄-alkylene or -O-CH₂-CH(OH)-CH₂ group, whilst the oxygen atom of the abovementioned groups in each case is linked to the bicyclic heteroaromatic ring,

5
10 B denotes an R_6O-CO -alkylene- NR_5 group wherein the alkylene moiety, which is straight-chained and contains 1 or 2 carbon atoms, may additionally be substituted by an R_6O-CO or R_6O-CO -methyl group, whilst

15 R_5 denotes a hydrogen atom,

a $C_{1,2}$ -alkyl group which may be substituted by an R_6O-CO group,

20 a $C_{2,4}$ -alkyl group which is substituted from position 2 onwards by a hydroxy group,

a $C_{3,6}$ -cycloalkyl or $C_{3,6}$ -cycloalkylmethyl group and

25 R_6 denotes a hydrogen atom,

30 a $C_{1,6}$ -alkyl, cyclopentyl, cyclopentylmethyl, cyclohexyl, cyclohexylmethyl, phenyl, benzyl, 5-indanyl or $R_6CO-O-(R_6CR_2)$ group, whilst

R_6 denotes a hydrogen atom or a $C_{1,4}$ -alkyl group,

35 R_7 denotes a hydrogen atom and

40 R_8 denotes a $C_{1,4}$ -alkyl, cyclopentyl, cyclohexyl, $C_{1,4}$ -alkoxy, cyclopentyloxy or cyclohexyloxy group,

a pyrrolidino or piperidino group which is substituted by an R_6O-CO or $R_6O-CO-C_{1,2}$ -alkyl group wherein R_6 is as hereinbefore defined,

45 a pyrrolidino or piperidino group which is substituted by two R_6O-CO or $R_6O-CO-C_{1,2}$ -alkyl groups wherein R_6 is as hereinbefore defined,

50

55

5 a piperazino group which is substituted in the 4 position by
the group R_{10} and additionally at a cyclic carbon atom by an
10 R_6O-CO or $R_6O-CO-C_{1,2}$ -alkyl group wherein R_6 is as hereinbefore
defined and

R_{10} denotes a hydrogen atom, a methyl or ethyl group,

15 a piperazino group which is substituted in the 4 position by an
 $R_6O-CO-C_{1,4}$ -alkyl, bis- $(R_6O-CO)-C_{1,4}$ -alkyl, $(R_7O-PO-OR_8)$ -methyl or
 $(R_7O-PO-R_9)$ -methyl group wherein R_6 is as hereinbefore defined,

20 R_7 and R_8 , which may be identical or different, in each
case denote a hydrogen atom, a methyl, ethyl, phenyl,
benzyl, 5-indanyl or $R_3CO-O-(R_4CR_5)$ group, whilst

25 R_4 to R_9 are as hereinbefore defined,

and R_9 denotes a methyl or ethyl group,

30 a piperazino group which is substituted in the 4 position by an
 $R_6O-CO-C_{1,2}$ -alkyl group and additionally at a cyclic carbon atom
by an R_6O-CO or $R_6O-CO-C_{1,2}$ -alkyl group wherein R_6 is as herein-
before defined,

35 a morpholino group which is substituted by an R_6O-CO or R_6O-CO-
 $C_{1,2}$ -alkyl group, whilst R_6 is as hereinbefore defined,

40 a pyrrolidinyl or piperidinyl group substituted in the 1 posi-
tion by an $R_6O-CO-C_{1,4}$ -alkyl, bis- $(R_6O-CO)-C_{1,4}$ -alkyl,
 $(R_7O-PO-OR_8)$ -methyl or $(R_7O-PO-R_9)$ -methyl group wherein R_6 to R_9
are as hereinbefore defined,

45 a 2-oxo-morpholino group which may be substituted by 1 or 2
methyl groups,

50 a 2-oxo-morpholinyl group which is substituted in the 4 posi-
tion by a methyl, ethyl or $R_6O-CO-C_{1,2}$ -alkyl group, whilst R_6 is

5 as hereinbefore defined and the abovementioned 2-oxo-morpholinyl groups in each case are linked to a carbon atom of the group A, or

10 a $R_{11}N(C_{1-2}\text{-alkyl})$ group wherein R_{11} denotes a 2-oxo-tetrahydrofuran-3-yl or 2-oxo-tetrahydrofuran-4-yl group, or

15 A and B together denote a hydrogen atom, a methoxy, ethoxy or 2-methoxy-ethoxy group,

20 a C_{1-2} -alkoxy group which is substituted by an $R_6O\text{-CO}$ group, whilst R_6 is as hereinbefore defined,

a C_{4-6} -cycloalkoxy or C_{3-6} -cycloalkyl- C_{1-3} -alkoxy group,

25 C denotes an $-O-C_{1-4}$ -alkylene or $-O-CH_2-CH(OH)-CH_2$ group, whilst the oxygen atom of the abovementioned groups in each case is linked to the bicyclic heteroaromatic ring,

30 D denotes an $R_9O\text{-CO-alkylene-NR}_5$ group wherein the alkylene moiety, which is straight-chained and contains 1 or 2 carbon atoms, may additionally be substituted by an $R_6O\text{-CO}$ or $R_6O\text{-CO-methyl}$ group, whilst R_5 and R_6 are as hereinbefore defined,

35 a pyrrolidino or piperidino group which is substituted by an $R_6O\text{-CO}$ or $R_6O\text{-CO-}C_{1-2}\text{-alkyl}$ group wherein R_6 is as hereinbefore defined,

40 a pyrrolidino or piperidino group which is substituted by two $R_6O\text{-CO}$ or $R_6O\text{-CO-}C_{1-2}\text{-alkyl}$ groups wherein R_6 is as hereinbefore defined,

45 a piperazino group which is substituted in the 4 position by the group R_{10} and additionally at a cyclic carbon atom by an $R_6O\text{-CO}$ or $R_6O\text{-CO-}C_{1-2}\text{-alkyl}$ group wherein R_6 and R_{10} are as
50 hereinbefore defined,

5 a piperazino group which is substituted in the 4 position by an
R₆O-CO-C₁₋₄-alkyl, bis-(R₆O-CO)-C₁₋₄-alkyl, (R₇O-PO-OR₈)-methyl or
10 (R₇O-PO-R₉)-methyl group wherein R₆ to R₉ are as hereinbefore
defined,

15 a piperazino group which is substituted in the 4 position by an
R₆O-CO-C₁₋₂-alkyl group and additionally at a cyclic carbon atom
by an R₆O-CO or R₆O-CO-C₁₋₂-alkyl group wherein R₆ is as herein-
before defined,

20 a morpholino group which is substituted by an R₆O-CO or R₆O-CO-
C₁₋₂-alkyl group, whilst R₆ is as hereinbefore defined,

25 a pyrrolidinyl or piperidinyl group substituted in the 1 posi-
tion by an R₆O-CO-C₁₋₄-alkyl, bis-(R₆O-CO)-C₁₋₄-alkyl, (R₇O-PO-
OR₈)-methyl or (R₇O-PO-R₉)-methyl group wherein R₆ to R₉ are as
hereinbefore defined,

30 a 2-oxo-morpholino group which may be substituted by 1 or 2
methyl groups,

35 a 2-oxo-morpholinyl group which is substituted in the 4 posi-
tion by a methyl, ethyl or R₆O-CO-C₁₋₂-alkyl group, whilst R₆ is
as hereinbefore defined and the abovementioned 2-oxo-morpholi-
nyl groups are in each case linked to a carbon atom of the
group C,

40 a R₁₁N(C₁₋₂-alkyl) group wherein R₁₁ denotes a 2-oxo-tetrahydro-
furan-3-yl or 2-oxo-tetrahydrofuran-4-yl group, or

45 C and D together denote a hydrogen atom, a methoxy, ethoxy or
2-methoxy-ethoxy group,

50 a C₁₋₂-alkoxy group which is substituted by an R₆O-CO group,
whilst R₆ is as hereinbefore defined,

55 a C₄₋₆-cycloalkoxy or C₃₋₆-cycloalkyl-C₁₋₃-alkoxy group

5

10

with the proviso that at least one of the groups B or D or A together with B or C together with D contains an optionally substituted 2-oxo-morpholinyl group, a $(R_7O-PO-OR_8)$ or $(R_7O-PO-R_9)$ group, or

15

20

that at least one of the groups A, B, C or D or A together with B or C together with D contains an R_6O-CO group and additionally one of the groups A, B, C or D or A together with B or C together with D contains a primary, secondary or tertiary amino function, whilst the nitrogen atom of this amino function is not linked to a carbon atom of an aromatic group,

the tautomers, stereoisomers and salts thereof.

25

Most particularly preferred compounds of general formula I are those wherein

30

R_a denotes a hydrogen atom,

35

R_b denotes a phenyl, benzyl or 1-phenylethyl group wherein the phenyl nucleus is substituted in each case by the groups R_1 to R_4 , whilst

40

R_1 and R_2 , which may be identical or different, each denote a hydrogen, fluorine, chlorine or bromine atom,

a methyl, trifluoromethyl, methoxy, ethynyl or cyano group and

45

R_3 denotes a hydrogen atom,

R_c and R_d in each case denote a hydrogen atom,

50

X denotes a nitrogen atom,

55

5 A denotes an $-O-C_{1-4}$ -alkylene or $-O-CH_2-CH(OH)-CH_2$ group, whilst
the oxygen atom of the abovementioned groups in each case is
10 linked to the bicyclic heteroaromatic ring,

B denotes an R_6O-CO -alkylene- NR_5 group wherein the alkylene
moiety, which is straight-chained and contains 1 or 2 carbon
15 atoms, may additionally be substituted by an R_6O-CO or R_6O-CO -
methyl group, whilst

R_5 denotes a hydrogen atom,

20 a C_{1-2} -alkyl group which may be substituted by an R_6O-CO
group,

25 a C_{2-4} -alkyl group which is substituted from position 2
onwards by a hydroxy group,

a C_{3-6} -cycloalkyl or C_{3-6} -cycloalkylmethyl group and

30 R_6 denotes a hydrogen atom,

a C_{1-6} -alkyl, cyclopentyl, cyclopentylmethyl, cyclohexyl,
35 cyclohexylmethyl, phenyl, benzyl, 5-indanyl or R_6CO-O-
(R_6CR_6) group, whilst

R_6 denotes a hydrogen atom or a C_{1-4} -alkyl group,

40 R_7 denotes a hydrogen atom and

R_8 denotes a C_{1-4} -alkyl, cyclopentyl, cyclohexyl,
45 C_{1-4} -alkoxy, cyclopentyloxy or cyclohexyloxy group,

a pyrrolidino or piperidino group which is substituted by an
 R_6O-CO or $R_6O-CO-C_{1-2}$ -alkyl group wherein R_6 is as hereinbefore
50 defined,

5 a pyrrolidino or piperidino group which is substituted by two
10 R_6O-CO or $R_6O-CO-C_{1-2}$ -alkyl groups wherein R_6 is as hereinbefore
defined,

15 a piperazino group which is substituted in the 4 position by
the group R_{10} and additionally at a cyclic carbon atom by an
 R_6O-CO or $R_6O-CO-C_{1-2}$ -alkyl group wherein R_6 is as hereinbefore
defined and

R_{10} denotes a hydrogen atom, a methyl or ethyl group,

20 a piperazino group which is substituted in the 4 position by an
 $R_6O-CO-C_{1-4}$ -alkyl, bis- $(R_6O-CO)-C_{1-4}$ -alkyl, $(R_7O-PO-OR_8)$ -methyl or
 $(R_7O-PO-R_9)$ -methyl group wherein R_6 is as hereinbefore defined,

25 R_7 and R_8 , which may be identical or different, in each
case denote a hydrogen atom, a methyl, ethyl, phenyl,
benzyl, 5-indanyl or $R_9CO-O-(R_9CR_9)$ group, whilst

30 R_6 to R_9 are as hereinbefore defined,

and R_9 denotes a methyl or ethyl group,

35 a piperazino group which is substituted in the 4 position by an
 $R_6O-CO-C_{1-2}$ -alkyl group and is additionally substituted at a
cyclic carbon atom by an R_6O-CO or $R_6O-CO-C_{1-2}$ -alkyl group
wherein R_6 is as hereinbefore defined,

40 a morpholino group which is substituted by an R_6O-CO or R_6O-CO-
 C_{1-2} -alkyl group, whilst R_6 is as hereinbefore defined,

45 a pyrrolidinyl or piperidinyl group substituted in the 1 posi-
tion by an $R_6O-CO-C_{1-4}$ -alkyl, bis- $(R_6O-CO)-C_{1-4}$ -alkyl,
 $(R_7O-PO-OR_8)$ -methyl or $(R_7O-PO-R_9)$ -methyl group wherein R_6 to R_9
are as hereinbefore defined,

50

55

5 a 2-oxo-morpholino group which may be substituted by 1 or 2
methyl groups,

10 a 2-oxo-morpholinyl group which is substituted in the 4 position by a methyl, ethyl or $R_6O-CO-C_{1-2}$ -alkyl group, whilst R_6 is as hereinbefore defined and the abovementioned 2-oxo-morpholinyl groups in each case are linked to a carbon atom of the
15 group A,

20 a $R_{11}N(C_{1-2}$ -alkyl) group wherein R_{11} denotes a 2-oxo-tetrahydrofuran-3-yl or 2-oxo-tetrahydrofuran-4-yl group, and

25 C and D together denote a hydrogen atom, a methoxy, ethoxy, 2-methoxy-ethoxy, C_{4-6} -cycloalkoxy or C_{3-6} -cycloalkyl- C_{1-3} -alkoxy group,

particularly those compounds wherein

30 R_1 denotes a hydrogen atom,

35 R_2 denotes a phenyl, benzyl or 1-phenylethyl group wherein the phenyl nucleus is substituted in each case by the groups R_1 to R_5 , whilst

R_1 and R_2 , which may be identical or different, each denote a hydrogen, fluorine, chlorine or bromine atom,

40 a methyl, trifluoromethyl, methoxy, ethynyl or cyano group and

45 R_3 denotes a hydrogen atom,

R_4 and R_5 in each case denote a hydrogen atom,

50 X denotes a nitrogen atom,

5
10 A and B together denote a hydrogen atom, a methoxy, ethoxy, 2-methoxy-ethoxy, C₄₋₆-cycloalkoxy or C₃₋₆-cycloalkyl-C₁₋₃-alkoxy group,

15 C denotes an -O-C₁₋₄-alkylene or -O-CH₂-CH(OH)-CH₂ group, whilst the oxygen atom of the abovementioned groups in each case is linked to the bicyclic heteroaromatic ring, and

20 D denotes an R₆O-CO-alkylene-NR₅ group wherein the alkylene moiety, which is straight-chained and contains 1 or 2 carbon atoms, may additionally be substituted by an R₆O-CO or R₆O-CO-methyl group, whilst

R₅ denotes a hydrogen atom,

25 a C₁₋₂-alkyl group which may be substituted by an R₆O-CO group,

30 a C₂₋₄-alkyl group which is substituted from position 2 by a hydroxy group,

a C₃₋₆-cycloalkyl or C₃₋₆-cycloalkylmethyl group and

35 R₆ denotes a hydrogen atom,

40 a C₁₋₆-alkyl, cyclopentyl, cyclopentylmethyl, cyclohexyl, cyclohexylmethyl, phenyl, benzyl, 5-indanyl or R₆CO-O-(R₆CR₆) group, whilst

R₆ denotes a hydrogen atom or a C₁₋₄-alkyl group,

45 R₇ denotes a hydrogen atom and

R₈ denotes a C₁₋₄-alkyl, cyclopentyl, cyclohexyl, C₁₋₄-alkoxy, cyclopentyloxy or cyclohexyloxy group,

50

55

5 a pyrrolidino or piperidino group which is substituted by an
R₆O-CO or R₆O-CO-C₁₋₂-alkyl group wherein R₆ is as hereinbefore
10 defined,

15 a pyrrolidino or piperidino group which is substituted by two
R₆O-CO or R₆O-CO-C₁₋₂-alkyl groups wherein R₆ is as hereinbefore
defined,

20 a piperazino group which is substituted in the 4 position by
the group R₁₀ and additionally at a cyclic carbon atom by an
R₆O-CO or R₆O-CO-C₁₋₂-alkyl group wherein R₆ is as hereinbefore
defined and

R₁₀ denotes a hydrogen atom, a methyl or ethyl group,

25 a piperazino group which is substituted in the 4 position by an
R₆O-CO-C₁₋₄-alkyl, bis-(R₆O-CO)-C₁₋₄-alkyl, (R₆O-PO-OR₆)-methyl or
(R₆O-PO-R₆)-methyl group wherein R₆ is as hereinbefore defined,

30 R₇ and R₈, which may be identical or different, in each
case denote a hydrogen atom, a methyl, ethyl, phenyl,
benzyl, 5-indanyl or R₉CO-O-(R₆CR₇) group, whilst

35 R₆ to R₉ are as hereinbefore defined,

and R₉ denotes a methyl or ethyl group,

40 a piperazino group which is substituted in the 4 position by an
R₆O-CO-C₁₋₂-alkyl group and is additionally substituted at a
cyclic carbon atom by an R₆O-CO or R₆O-CO-C₁₋₂-alkyl group
wherein R₆ is as hereinbefore defined,

45 a morpholino group which is substituted by an R₆O-CO or R₆O-CO-
C₁₋₃-alkyl group, whilst R₆ is as hereinbefore defined,

50 a pyrrolidinyl or piperidinyl group substituted in the 1 posi-
tion by an R₆O-CO-C₁₋₄-alkyl, bis-(R₆O-CO)-C₁₋₄-alkyl,

(R₇O-PO-OR₈)-methyl or (R₇O-PO-R₈)-methyl group wherein R₆ to R₈ are as hereinbefore defined,

a 2-oxo-morpholino group which may be substituted by 1 or 2 methyl groups,

a 2-oxo-morpholinyl group which is substituted in the 4 position by a methyl, ethyl or R₆O-CO-C₁₋₃-alkyl group, whilst R₆ is as hereinbefore defined and the abovementioned 2-oxo-morpholinyl groups are in each case linked to a carbon atom of the group C, or

a R₁₁N(C₁₋₃-alkyl) group wherein R₁₁ denotes a 2-oxo-tetrahydrofuran-3-yl or 2-oxo-tetrahydrofuran-4-yl group,

the tautomers, stereoisomers and salts thereof.

The most preferred bicyclic heterocyclic compounds of general formula I, however, are those wherein

R_a denotes a hydrogen atom,

R_b denotes a phenyl group wherein the phenyl nucleus is substituted in each case by the groups R₁ to R₃, whilst

R₁ and R₂, which may be identical or different, each denote a hydrogen, fluorine, chlorine or bromine atom and

R₃ denotes a hydrogen atom,

R_c and R_d in each case denote a hydrogen atom,

X denotes a nitrogen atom,

A denotes an -O-C₁₋₄-alkylene or -O-CH₂-CH(OH)-CH₂ group, whilst the oxygen atom of the abovementioned groups in each case is linked to the bicyclic heteroaromatic ring,

B denotes an $R_4O-CO-CH_2-NR_5$ group wherein

R_5 denotes a hydrogen atom or a methyl group which may be substituted by an R_6O-CO group, or

a C_{2-4} -alkyl group substituted from position 2 onwards by a hydroxy group, and

R_6 denotes a hydrogen atom, a methyl or ethyl group,

a pyrrolidino or piperidino group which is substituted by an R_6O-CO group, whilst R_6 is as hereinbefore defined,

a piperazino group which is substituted in the 4 position by an $R_6O-CO-CH_2$ or bis- $(R_6O-CO)-C_{1-3}$ -alkyl group, whilst R_6 is as hereinbefore defined,

a pyrrolidinyl or piperidinyl group substituted in the 1 position by an $R_6O-CO-CH_2$ group, whilst R_6 is as hereinbefore defined,

a 2-oxo-morpholino group which may be substituted by one or two methyl groups, or

a $R_{11}N(C_{1-2}$ -alkyl) group wherein R_{11} denotes a 2-oxo-tetrahydrofuran-3-yl or 2-oxo-tetrahydrofuran-4-yl group, and

C and D together denote a methoxy, C_{4-6} -cycloalkoxy or C_{3-6} -cycloalkylmethoxy group,

particular those compounds wherein

R_3 denotes a hydrogen atom,

R_6 denotes a phenyl group wherein the phenyl nucleus is substituted in each case by the groups R_1 to R_5 , whilst

R_1 and R_2 , which may be identical or different, each denote a hydrogen, fluorine, chlorine or bromine atom and

R_3 denotes a hydrogen atom,

R_c and R_d in each case denote a hydrogen atom,

X denotes a nitrogen atom,

A and B together denote a C_{1-6} -cycloalkoxy or C_{1-6} -cycloalkyl-methoxy group,

C denotes an $-O-CH_2CH_2$ group, whilst the oxygen atom of the abovementioned group is linked to the bicyclic heteroaromatic ring,

D denotes an $R_eO-CO-CH_2-NR_f$ group wherein

R_g denotes a C_{2-4} -alkyl group substituted from position 2 onwards by a hydroxy group, and

R_h denotes a methyl or ethyl group,

a 2-oxo-morpholino group which may be substituted by one or two methyl groups, or

a $R_{11}N(C_{1-2}$ -alkyl) group wherein R_{11} denotes a 2-oxo-tetrahydrofuran-3-yl or 2-oxo-tetrahydrofuran-4-yl group,

the tautomers, stereoisomers and salts thereof.

The following particularly preferred compounds of general formula I are mentioned by way of example:

(1) 4-(3-chloro-4-fluorophenylamino)-6-{3-[4-(methoxycarbonylmethyl)-1-piperazinyl]propyloxy}-7-methoxy-quinazoline,

(2) 4-[(3-bromophenyl)amino]-6-(2-{4-[(ethoxycarbonyl)methyl]-piperazin-1-yl}ethoxy)-7-methoxy-quinazoline,

(3) (S)-4-[(3-bromophenyl)amino]-6-[3-(2-methoxycarbonyl-pyrrolidin-1-yl)propyloxy]-7-methoxy-quinazoline,

(4) 4-[(3-bromophenyl)amino]-6-(3-{4-[(ethoxycarbonyl)methyl]-piperazin-1-yl}-2-hydroxy-propyloxy)-7-methoxy-quinazoline,

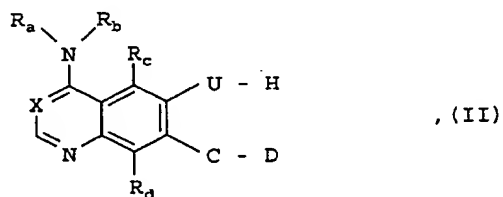
(5) (S)-4-[(3-bromophenyl)amino]-6-({1-[(ethoxycarbonyl)methyl]-pyrrolidine-2-yl}methoxy)-7-methoxy-quinazoline and

(6) 4-[(3-bromophenyl)amino]-6-(2-{4-[1,2 bis(methoxycarbonyl)-ethyl]-piperazin-1-yl}ethoxy)-7-methoxy-quinazoline

and the salts thereof.

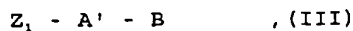
The compounds of general formula I may, for example, be prepared by the following methods:

a) reacting a compound of general formula



wherein

R_a to R_d, C, D and X are as hereinbefore defined and U denotes an oxygen atom or an R_aN group, whilst R_a is as hereinbefore defined, with a compound of general formula



wherein

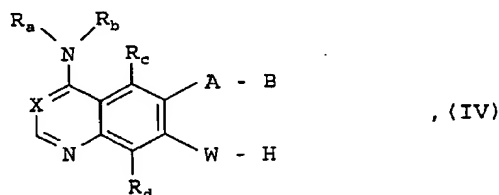
B is as hereinbefore defined,

A' denotes one of the optionally substituted alkylene, cycloalkylene, alkylene-cycloalkylene, cycloalkylene-alkylene or alkylene-cycloalkylene-alkylene moieties mentioned above for the group A, which are linked to the heteroaromatic group via an oxygen atom or via an NR₁ group, and

Z₁ denotes a leaving group such as a halogen atom or a sulphonyloxy group such as a chlorine or bromine atom, a methanesulphonyloxy or p-toluenesulphonyloxy group.

The reaction is optionally carried out in a solvent or mixture of solvents such as methylene chloride, dimethylformamide, dimethylsulphoxide, sulfolane, benzene, toluene, chlorobenzene, tetrahydrofuran, benzene/tetrahydrofuran or dioxane conveniently in the presence of a tertiary organic base such as triethylamine, pyridine or 2-dimethylaminopyridine, in the presence of N-ethyl-diisopropylamine (Hünig's base), whilst these organic bases may simultaneously serve as solvents, or in the presence of an inorganic base such as sodium carbonate, potassium carbonate or sodium hydroxide solution conveniently at temperatures between -20 and 200°C, preferably at temperatures between 0 and 150°C.

b) reacting a compound of general formula



wherein

R_a to R_d, A, B and X are as hereinbefore defined and

W denotes an oxygen atom or an R₁N group, whilst R₁ is as hereinbefore defined, with a compound of general formula



wherein

D is as hereinbefore defined,

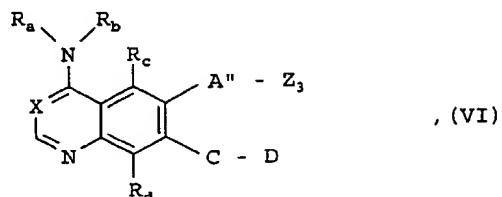
C' denotes one of the optionally substituted alkylene, cycloalkylene, alkylene-cycloalkylene, cycloalkylene-alkylene or alkylene-cycloalkylene-alkylene moieties mentioned above for the group C, which are linked to the heteroaromatic group via an oxygen atom or via an NR₄ group, and

Z₂ denotes a leaving group such as a halogen atom or a sulphonyloxy group such as a chlorine or bromine atom, a methanesulphonyloxy or p-toluenesulphonyloxy group.

The reaction is optionally carried out in a solvent or mixture of solvents such as methylene chloride, dimethylformamide, dimethylsulphoxide, sulpholane, benzene, toluene, chlorobenzene, tetrahydrofuran, benzene/tetrahydrofuran or dioxane conveniently in the presence of a tertiary organic base such as triethylamine, pyridine or 2-dimethylaminopyridine, in the presence of N-ethyl-diisopropylamine (Hünig's base), whilst these organic bases may simultaneously serve as solvents, or in the presence of an inorganic base such as sodium carbonate, potassium carbonate or sodium hydroxide solution or in the presence of an alkali or alkaline earth metal alkoxide such as sodium ethoxide or potassium tert.butoxide conveniently at temperatures between -20 and 200°C, preferably at temperatures between 0 and 150°C.

c) In order to prepare a compound of general formula I wherein A is as hereinbefore defined with the exception of the oxygen atom and the -NR₄ group:

reacting a compound of general formula



wherein

R_a to R_d , C, D and X are as hereinbefore defined and
 A'' has the meanings given for A hereinbefore with the exception
of the oxygen atom and the $-NR$ group and
 Z_3 denotes a leaving group such as a halogen atom or a sulphonyloxy group such as a chlorine or bromine atom, a methanesulphonyloxy or p-toluenesulphonyloxy group or together with a hydrogen atom of an adjacent hydrocarbon group denotes an oxygen atom, with a compound of general formula



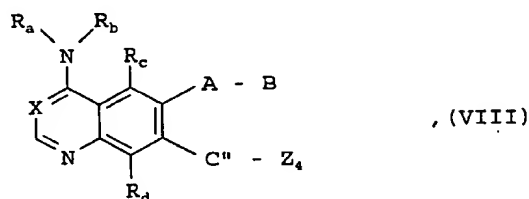
wherein

B is as hereinbefore defined.

The reaction is optionally carried out in a solvent or mixture of solvents such as acetonitrile, ethanol, methylene chloride, dimethylformamide, dimethylsulphoxide, sulpholane, benzene, toluene, chlorobenzene, tetrahydrofuran, benzene/tetrahydrofuran or dioxane, optionally in the presence of a tertiary organic base such as triethylamine, pyridine or 2-dimethylaminopyridine, in the presence of N-ethyl-diisopropylamine (Hünig's base), whilst these organic bases may simultaneously serve as solvents, or in the presence of an inorganic base such as sodium carbonate, potassium carbonate or sodium hydroxide solution or in the presence of an alkali or alkaline earth metal alkoxide such as sodium ethoxide or potassium tert.but-oxide, conveniently at temperatures between -20 and 200°C , preferably at temperatures between 0 and 150°C .

d) In order to prepare a compound of general formula I wherein C is as hereinbefore defined with the exception of the oxygen atom and the $-NR_4$ group:

reacting a compound of general formula



wherein

C'' has the meanings given for C hereinbefore with the exception of the oxygen atom and the $-NR_4$ group and

Z₄ denotes a leaving group such as a halogen atom or a sulphonyloxy group such as a chlorine or bromine atom, a methanesulphonyloxy or p-toluenesulphonyloxy group or together with a hydrogen atom of an adjacent hydrocarbon group denotes an oxygen atom, with a compound of general formula



wherein

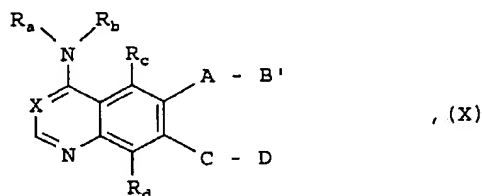
D is as hereinbefore defined.

The reaction is optionally carried out in a solvent or mixture of solvents such as acetonitrile, ethanol, methylene chloride, dimethylformamide, dimethylsulphoxide, sulpholane, benzene, toluene, chlorobenzene, tetrahydrofuran, benzene/tetrahydrofuran or dioxane optionally in the presence of a tertiary organic base such as triethylamine, pyridine or 2-dimethylaminopyridine, in the presence of N-ethyl-diisopropylamine (Hünig's base), whilst these organic bases may simultaneously serve as solvents, or in the presence of an inorganic base such as sodium carbonate, potassium carbonate or sodium hydroxide

solution or in the presence of an alkali or alkaline earth metal alkoxide such as sodium ethoxide or potassium tert.but-oxide, conveniently at temperatures between -20 and 200°C, preferably at temperatures between 0 and 150°C.

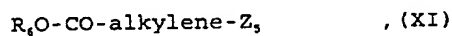
e) In order to prepare a compound of general formula I wherein B denotes an R_6O-CO -alkylene- NR_5 group wherein the alkylene moiety, which is straight-chained and contains 1 to 6 carbon atoms, may additionally be substituted by one or two C_{1-2} -alkyl groups or by an R_6O-CO or $R_6O-CO-C_{1-2}$ -alkyl group, a piperazino or homopiperazino group substituted in the 4 position by an $R_6O-CO-C_{1-4}$ -alkyl or bis- $(R_6O-CO)-C_{1-4}$ -alkyl group or a pyrrolidinyl, piperidinyl or hexahydroazepinyl group substituted in the 1 position by an $R_6O-CO-C_{1-4}$ -alkyl or bis- $(R_6O-CO)-C_{1-4}$ -alkyl group, whilst in each case R_5 and R_6 are as hereinbefore defined:

reacting a compound of general formula



wherein

R_a to R_d , A, C, D and X are as hereinbefore defined and B' denotes an R_5NH group wherein R_5 is as hereinbefore defined, a piperazino or homopiperazino group unsubstituted in the 4 position, a pyrrolidinyl, piperidinyl or hexahydroazepinyl group unsubstituted in the 1 position, with a compound of general formula



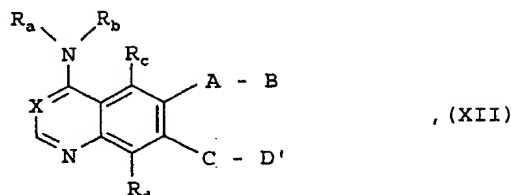
wherein

the alkylene moiety, which is straight-chained and contains 1 to 6 carbon atoms, may additionally be substituted by one or two C_{1-2} -alkyl groups or by an R_6O-CO or $R_6O-CO-C_{1-2}$ -alkyl group, whilst R_6 in each case is as hereinbefore defined, and Z_6 denotes an exchangeable group such as a halogen atom or a substituted sulphonyloxy group, e.g. a chlorine or bromine atom, a methylsulphonyloxy, propylsulphonyloxy, phenylsulphonyloxy or benzylsulphonyloxy group.

The reaction is optionally carried out in a solvent or mixture of solvents such as acetonitrile, methylene chloride, dimethylformamide, dimethylsulphoxide, sulpholane, benzene, toluene, chlorobenzene, tetrahydrofuran, benzene/tetrahydrofuran or dioxane conveniently in the presence of a tertiary organic base such as triethylamine or N-ethyl-diisopropylamine (Hünig's base), whilst these organic bases may simultaneously serve as solvents, or in the presence of an inorganic base such as sodium carbonate, potassium carbonate or sodium hydroxide solution conveniently at temperatures between -20 and $200^\circ C$, preferably at temperatures between 0 and $150^\circ C$.

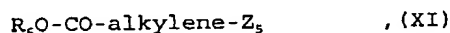
f) In order to prepare a compound of general formula I wherein D denotes an R_6O-CO -alkylene- NR_7 group wherein the alkylene moiety, which is straight-chained and contains 1 to 6 carbon atoms, may additionally be substituted by one or two C_{1-2} -alkyl groups or by an R_6O-CO or $R_6O-CO-C_{1-2}$ -alkyl group, a piperazino or homopiperazino group substituted in the 4 position by an $R_6O-CO-C_{1-4}$ -alkyl or bis- $(R_6O-CO)-C_{1-4}$ -alkyl group or a pyrrolidinyl, piperidinyl or hexahydroazepinyl group substituted in the 1 position by an $R_6O-CO-C_{1-4}$ -alkyl or bis- $(R_6O-CO)-C_{1-4}$ -alkyl group, whilst in each case R_6 and R_7 are as hereinbefore defined:

reacting a compound of general formula



wherein

R_a to R_d , A to C and X are as hereinbefore defined and D' denotes an R_sNH group wherein R_s is as hereinbefore defined, a piperazino or homopiperazino group unsubstituted in the 4 position, a pyrrolidinyl, piperidinyl or hexahydroazepinyl group unsubstituted in the 1 position, with a compound of general formula



wherein

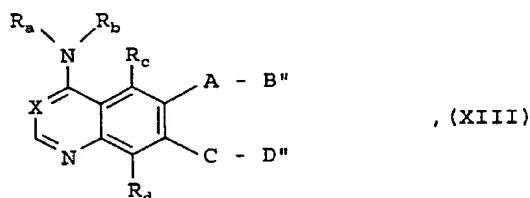
the alkylene moiety, which is straight-chained and contains 1 to 6 carbon atoms, may additionally be substituted by one or two C_{1-2} -alkyl groups or by an R_6O-CO or $R_6O-CO-C_{1-2}$ -alkyl group, whilst R_6 in each case is as hereinbefore defined, and Z_s denotes an exchangeable group such as a halogen atom or a substituted sulphonyloxy group, e.g. a chlorine or bromine atom, a methylsulphonyloxy, propylsulphonyloxy, phenylsulphonyloxy or benzylsulphonyloxy group.

The reaction is optionally carried out in a solvent or mixture of solvents such as acetonitrile, methylene chloride, dimethylformamide, dimethylsulphoxide, sulpholane, benzene, toluene, chlorobenzene, tetrahydrofuran, benzene/tetrahydrofuran or dioxane conveniently in the presence of a tertiary organic base such as triethylamine or N-ethyl-diisopropylamine (Hünig's base), whilst these organic bases may simultaneously serve as solvents, or in the presence of an inorganic base such as

sodium carbonate, potassium carbonate or sodium hydroxide solution conveniently at temperatures between -20 and 200°C, preferably at temperatures between 0 and 150°C.

g) In order to prepare a compound of general formula I wherein at least one of the groups R_6 to R_8 denotes a hydrogen atom:

Converting a compound of general formula



wherein

R_a to R_d , A, C and X are as hereinbefore defined, B" and D" have the meanings given for B and D hereinbefore, with the proviso that at least one of the groups B" or D" contains an R_6O-CO , $(R_7O-PO-OR_8)$ or $(R_7O-PO-R_9)$ group wherein R_6 is as hereinbefore defined and at least one of the groups R_6 to R_8 does not represent a hydrogen atom, by hydrolysis, treating with acids, thermolysis or hydrogenolysis, into a compound of general formula I wherein at least one of the groups R_6 to R_8 denotes a hydrogen atom.

The hydrolysis is conveniently carried out either in the presence of an acid such as hydrochloric acid, sulphuric acid, phosphoric acid, acetic acid, trichloroacetic acid, trifluoroacetic acid or mixtures thereof or in the presence of a base such as lithium hydroxide, sodium hydroxide or potassium hydroxide in a suitable solvent such as water, water/methanol, water/ethanol, water/isopropanol, methanol, ethanol, water/tetrahydrofuran or water/dioxane at temperatures between -10 and 120°C, e.g. at temperatures between ambient temperature and the boiling temperature of the reaction mixture.

5
10
15
20
25
30
If B" or D" in a compound of formula X for example contains the tert.butyloxycarbonyl group, the tert.butyl group may also be cleaved by treating with an acid such as trifluoroacetic acid, formic acid, p-toluenesulphonic acid, sulphuric acid, hydrochloric acid, phosphoric acid or polyphosphoric acid optionally in an inert solvent such as methylene chloride, chloroform, benzene, toluene, diethylether, tetrahydrofuran or dioxane preferably at temperatures between -10 and 120°C, e.g. at temperatures between 0 and 60°C, or thermally, optionally in an inert solvent such as methylene chloride, chloroform, benzene, toluene, tetrahydrofuran or dioxane and preferably in the presence of a catalytic amount of an acid such as p-toluenesulphonic acid, sulphuric acid, phosphoric acid or polyphosphoric acid preferably at the boiling temperature of the solvent used, e.g. at temperatures between 40 and 120°C. Under the reaction conditions mentioned above, any N-tert.butyloxycarbonylamino or N-tert.butyloxycarbonylimino groups present may be converted into the corresponding amino or imino groups.

35
40
45
If B" or D" in a compound of formula X for example contains the benzyloxycarbonyl group, the benzyl group may also be cleaved hydrogenolytically in the presence of a hydrogenation catalyst such as palladium/charcoal in a suitable solvent such as methanol, ethanol, ethanol/water, glacial acetic acid, ethyl acetate, dioxane or dimethylformamide, preferably at temperatures between 0 and 50°C, e.g. ambient temperature, and at a hydrogen pressure of 1 to 5 bar. During the hydrogenolysis other groups may simultaneously be converted, e.g. a nitro group may be converted into an amino group, a benzyloxy group into a hydroxy group and a N-benzylamino, N-benzylimino, N-benzyloxycarbonylamino or N-benzyloxycarbonylimino group into a corresponding amino or imino group.

50
55
If according to the invention a compound of general formula I is obtained which contains a carboxy or hydroxyphosphoryl

5

- 52 -

group, this may be converted by esterification into a corresponding ester of general formula I or

10

If a compound of general formula I is obtained wherein B or D denotes an optionally substituted N-(2-hydroxyethyl)-glycine or N-(2-hydroxyethyl)-glycinester group, this may be converted by cyclisation in a corresponding 2-oxo-morpholino compound.

15

The subsequent esterification is optionally carried out in a solvent or mixture of solvents such as methylene chloride, dimethylformamide, benzene, toluene, chlorobenzene, tetrahydrofuran, benzene/tetrahydrofuran or dioxane or particularly advantageously in a corresponding alcohol, optionally in the presence of an acid such as hydrochloric acid or in the presence of a dehydrating agent, e.g. in the presence of isobutyl chloroformate, thionylchloride, trimethylchlorosilane, sulphuric acid, methanesulphonic acid, p-toluenesulphonic acid, phosphorus trichloride, phosphorus pentoxide, N,N'-dicyclohexylcarbodiimide, N,N'-dicyclohexylcarbodiimide/N-hydroxysuccinimide or 1-hydroxy-benzotriazole and optionally additionally in the presence of 4-dimethylamino-pyridine, N,N'-carbonyldiimidazole or triphenyl-phosphine/carbon tetrachloride, conveniently at temperatures between 0 and 150°C, preferably at temperatures between 0 and 80°C.

20

25

30

35

The subsequent ester formation may also be carried out by reacting a compound which contains a carboxy or hydroxy-phosphoryl group with a corresponding alkyl halide.

40

The subsequent intramolecular cyclisation is optionally carried out in a solvent or mixture of solvents such as acetonitrile, methylene chloride, tetrahydrofuran, dioxane or toluene in the presence an acid such as hydrochloric acid or p-toluenesulphonic acid at temperatures between -10 and 120°C.

45

In the reactions described hereinbefore, any reactive groups present such as hydroxy, carboxy, phosphono, O-alkyl-phosphono,

50

55

5 amino, alkylamino or imino groups may be protected during the
reaction by conventional protecting groups which are cleaved
10 again after the reaction.

For example, a protecting group for a hydroxy group may be a
trimethylsilyl, acetyl, benzoyl, methyl, ethyl, tert.butyl,
15 trityl, benzyl or tetrahydropyranyl group.

protecting groups for a carboxy group may be a trimethylsilyl,
methyl, ethyl, tert.butyl, benzyl or tetrahydropyranyl group,

20 protecting groups for a phosphono group may be an alkyl group
such as the methyl, ethyl, isopropyl or n-butyl group, the
phenyl or benzyl group, and

25 protecting groups for an amino, alkylamino or imino group may
be a formyl, acetyl, trifluoroacetyl, ethoxycarbonyl, tert.but-
oxycarbonyl, benzyloxycarbonyl, benzyl, methoxybenzyl or
30 2,4-dimethoxybenzyl group and additionally, for the amino
group, a phthalyl group.

Any protecting group used is optionally subsequently cleaved
for example by hydrolysis in an aqueous solvent, e.g. in water,
35 isopropanol/water, acetic acid/water, tetrahydrofuran/water or
dioxane/water, in the presence of an acid such as trifluoroace-
tic acid, hydrochloric acid or sulphuric acid or in the pre-
sence of an alkali metal base such as sodium hydroxide or
40 potassium hydroxide or aprotically, e.g. in the presence of
iodotrimethylsilane, at temperatures between 0 and 120°C,
preferably at temperatures between 10 and 100°C.

45 However, a benzyl, methoxybenzyl or benzyloxycarbonyl group is
cleaved, for example, hydrogenolytically, e.g. with hydrogen in
the presence of a catalyst such as palladium/charcoal in a sui-
table solvent such as methanol, ethanol, ethyl acetate or gla-
50 cial acetic acid, optionally with the addition of an acid such
as hydrochloric acid at temperatures between 0 and 100°C, but

preferably at temperatures between 20 and 60°C, and at a hydrogen pressure of 1 to 7 bar, but preferably 3 to 5 bar. A 2,4-dimethoxybenzyl group, however, is preferably cleaved in trifluoroacetic acid in the presence of anisole.

A tert.butyl or tert.butyloxycarbonyl group is preferably cleaved by treating with an acid such as trifluoroacetic acid or hydrochloric acid or by treating with iodotrimethylsilane optionally using a solvent such as methylene chloride, dioxane, methanol or diethylether.

A trifluoroacetyl group is preferably cleaved by treating with an acid such as hydrochloric acid, optionally in the presence of a solvent such as acetic acid at temperatures between 50 and 120°C or by treating with sodium hydroxide solution optionally in the presence of a solvent such as tetrahydrofuran at temperatures between 0 and 50°C.

A phthalyl group is preferably cleaved in the presence of hydrazine or a primary amine such as methylamine, ethylamine or n-butylamine in a solvent such as methanol, ethanol, isopropanol, toluene/water or dioxane at temperatures between 20 and 50°C.

A single alkyl group may be cleaved from an O,O'-dialkylphosphono group with sodium iodide, for example, in a solvent such as acetone, methylethylketone, acetonitrile or dimethylformamide at temperatures between 40 and 150°C, but preferably at temperatures between 60 and 100°C.

Both alkyl groups may be cleaved from an O,O'-dialkyl-phosphono group with iodotrimethylsilane, bromotrimethylsilane or chlorotrimethylsilane/sodium iodide, for example, in a solvent such as methylene chloride, chloroform or acetonitrile at temperatures between 0°C and the boiling temperature of the reaction mixture, but preferably at temperatures between 20 and 60°C.

5

- 55 -

10

Moreover, the compounds of general formula I obtained may be resolved into their enantiomers and/or diastereomers, as mentioned hereinbefore. Thus, for example, cis/trans mixtures may be resolved into their cis and trans isomers, and compounds with at least one optically active carbon atom may be separated into their enantiomers.

15

20

Thus, for example, the cis/trans mixtures may be resolved by chromatography into the cis and trans isomers thereof, the compounds of general formula I obtained which occur as racemates may be separated by methods known *per se* (cf. Allinger N. L. and Eliel E. L. in "Topics in Stereochemistry", Vol. 6, Wiley Interscience, 1971) into their optical antipodes and compounds of general formula I with at least 2 asymmetric carbon atoms may be resolved into their diastereomers on the basis of their physical-chemical differences using methods known *per se*, e.g. by chromatography and/or fractional crystallisation, and, if these compounds are obtained in racemic form, they may subsequently be resolved into the enantiomers as mentioned above.

25

30

35

40

45

50

The enantiomers are preferably separated by column separation on chiral phases or by recrystallisation from an optically active solvent or by reacting with an optically active substance which forms salts or derivatives such as e.g. esters or amides with the racemic compound, particularly acids and the activated derivatives or alcohols thereof, and separating the diastereomeric mixture of salts or derivatives thus obtained, e.g. on the basis of their differences in solubility, whilst the free antipodes may be released from the pure diastereomeric salts or derivatives by the action of suitable agents. Optically active acids in common use are e.g. the D- and L-forms of tartaric acid or dibenzoyltartaric acid, di-o-tolytartaric acid, malic acid, mandelic acid, camphorsulphonic acid, glutamic acid, aspartic acid or quinic acid. An optically active alcohol may be for example (+) or (-)-menthol and an optically

55

5

- 56 -

active acyl group in amides, for example, may be a (+)-or
(-)-menthyloxycarbonyl.

10

Furthermore, the compounds of formula I may be converted into
the salts thereof, particularly for pharmaceutical use into the
physiologically acceptable salts with inorganic or organic
acids. Acids which may be used for this purpose include for
example hydrochloric acid, hydrobromic acid, sulphuric acid,
phosphoric acid, fumaric acid, succinic acid, lactic acid,
citric acid, tartaric acid or maleic acid.

15

20

Moreover, if the new compounds of formula I thus obtained
contain a carboxy, hydroxyphosphoryl, sulpho or 5-tetrazolyl
group, they may subsequently, if desired, be converted into the
salts thereof with inorganic or organic bases, particularly for
pharmaceutical use into the physiologically acceptable salts
thereof. Suitable bases for this purpose include for example
sodium hydroxide, potassium hydroxide, arginine, cyclohexyl-
amine, ethanolamine, diethanolamine and triethanolamine.

25

30

The compounds of general formulae II to XIII used as starting
materials are known from the literature in some cases or may be
obtained by methods known from the literature (cf. Examples I
to XVI).

35

As already mentioned hereinbefore, the compounds of general
formula I according to the invention and their physiologically
acceptable salts have valuable pharmacological properties,
particularly an inhibiting effect on signal transduction
mediated by the Epidermal Growth Factor receptor (EGF-R),
whilst this may be achieved for example by inhibiting ligand
bonding, receptor dimerisation or tyrosine kinase itself. It
is also possible to block the transmission of signals to com-
ponents located further down.

40

45

50

The biological properties of the new compounds were investiga-
ted as follows:

55

5

- 57 -

10

15

20

The inhibition of the EGF-R-mediated signal transmission can be demonstrated e.g. with cells which express human EGF-R and whose survival and proliferation depend on stimulation by EGF or TGF- α . A cell line of murine origin dependent on interleukin-3-(IL-3) which was genetically modified to express functional human EGF-R was used here. The proliferation of these cells known as F/L-HERc can therefore be stimulated either by murine IL-3 or by EGF (cf. von Rüden, T. et al. in EMBO J. 7, 2749-2756 (1988) and Pierce, J. H. et al. in Science 239, 628-631 (1988)).

25

30

35

40

The starting material used for the F/L-HERc cells was the cell line FDC-P₁, the production of which has been described by Dexter, T. M. et al. in J. Exp. Med. 152, 1036-1047 (1980). Alternatively, however, other growth-factor-dependent cells may also be used (cf. for example Pierce, J. H. et al. in Science 239, 628-631 (1988), Shibuya, H. et al. in Cell 70, 57-67 (1992) and Alexander, W. S. et al. in EMBO J. 10, 3683-3691 (1991)). For expressing the human EGF-R cDNA (cf. Ullrich, A. et al. in Nature 309, 418-425 (1984)) recombinant retroviruses were used as described by von Rüden, T. et al., EMBO J. 7, 2749-2756 (1988), except that the retroviral vector LXSN (cf. Miller, A. D. et al. in BioTechniques 7, 980-990 (1989)) was used for the expression of the EGF-R cDNA and the line GP+E86 (cf. Markowitz, D. et al. in J. Virol. 62, 1120-1124 (1988)) was used as the packaging cell.

The test was performed as follows:

45

50

55

F/L-HERc cells were cultivated in RPMI/1640 medium (BioWhittaker), supplemented with 10 % foetal calf serum (FCS, Boehringer Mannheim), 2 mM glutamine (BioWhittaker), standard antibiotics and 20 ng/ml of human EGF (Promega), at 37°C and 5% CO₂. In order to investigate the inhibitory activity of the compounds according to the invention, 1.5×10^4 cells per well were cultivated in triplicate in 96-well dishes in the above

medium (200 μ l), the cell proliferation being stimulated with either EGF (20 ng/ml) or murine IL-3. The IL-3 used was obtained from culture supernatants of the cell line X63/0 mIL-3 (cf. Karasuyama, H. et al. in Eur. J. Immunol. 18, 97-104 (1988)). The compounds according to the invention were dissolved in 100% dimethylsulphoxide (DMSO) and added to the cultures in various dilutions, the maximum DMSO concentration being 1%. The cultures were incubated for 48 hours at 37°C.

In order to determine the inhibitory activity of the compounds according to the invention the relative cell number was measured in O.D. units using the Cell Titer 96TM Aqueous Non-Radioactive Cell Proliferation Assay (Promega). The relative cell number was calculated as a percentage of the control (F/LHERc cells without inhibitor) and the concentration of active substance which inhibits the proliferation of the cells by 50% (IC₅₀) was derived therefrom. The following results were obtained:

Compound (Example no.)	Inhibition of EGF- dependent proliferation IC ₅₀ [nM]
1	46
1 (2)	20
2	230
2 (1)	39
3	45
3 (1)	100
3 (2)	70
3 (4)	77
4	33

The compounds of general formula I according to the invention thus inhibit the signal transduction by tyrosine kinases, as demonstrated by the example of the human EGF receptor, and are

5

- 59 -

10

therefore useful for treating pathophysiological processes caused by hyperfunction of tyrosinekinases. These are e.g. benign or malignant tumours, particularly tumours of epithelial and neuroepithelial origin, metastatisation and the abnormal proliferation of vascular endothelial cells (neovascularization).

15

20

25

The compounds according to the invention are also useful for preventing and treating diseases of the airways and lungs which are accompanied by increased or altered production of mucus caused by stimulation by tyrosinekinases, e.g. in inflammatory diseases of the airways such as chronic bronchitis, chronic obstructive bronchitis, asthma, bronchiectasias, allergic or non-allergic rhinitis or sinusitis, cystic fibrosis, α 1-antitrypsin deficiency, or coughs, pulmonary emphysema, pulmonary fibrosis and hyperreactive airways.

30

35

40

45

The compounds are also suitable for treating diseases of the gastrointestinal tract and bile duct and gall bladder which are associated with disrupted activity of the tyrosinekinases, such as may be found e.g. in chronic inflammatory changes such as cholecystitis, Crohn's disease, ulcerative colitis, and ulcers in the gastrointestinal tract or such as may occur in diseases of the gastrointestinal tract which are associated with increased secretions, such as Ménétrier's disease, secreting adenomas and protein loss syndrome, and also for treating nasal polyps and polyps of the gastrointestinal tract of various origins such as e.g. villous or adenomatous polyps of the large bowel, but also polyps in familial polyposis coli, intestinal polyps in Gardner's syndrome, polyps throughout the entire gastrointestinal tract in Peutz-Jeghers syndrome, in inflammatory pseudopolyps, juvenile polyps, Colitis cystica profunda and Pneumatosis cystoides intestinales.

50

Moreover, the compounds of general formula I and the physiologically acceptable salts thereof may be used to treat kidney diseases, particularly in cystic changes such as cystic kid-

55

5

- 60 -

10

15

neys, for treating renal cysts which may be idiopathic in origin or occur in syndromes such as e.g. tuberculous sclerosis, in von-Hippel-Lindau Syndrome, in nephronophthisis and spongy kidney and other diseases caused by aberrant function of tyrosinekinases, such as e.g. epidermal hyperproliferation (psoriasis), inflammatory processes, diseases of the immune system, hyperproliferation of haematopoietic cells, etc.

20

25

30

35

40

By reason of their biological properties the compounds according to the invention may be used on their own or in conjunction with other pharmacologically active compounds, for example in tumour therapy, in monotherapy or in conjunction with other anti-tumour therapeutic agents, for example in combination with topoisomerase inhibitors (e.g. etoposide), mitosis inhibitors (e.g. vinblastin), compounds which interact with nucleic acids (e.g. cis-platin, cyclophosphamide, adriamycin), hormone antagonists (e.g. tamoxifen), inhibitors of metabolic processes (e.g. 5-FU etc.), cytokines (e.g. interferons), antibodies, etc. For treating respiratory tract diseases, these compounds may be used on their own or in conjunction with other therapeutic agents for the airways, such as substances with a secretolytic, broncholytic and/or anti-inflammatory activity. For treating diseases in the region of the gastrointestinal tract, these compounds may also be administered on their own or in conjunction with substances having an effect on motility or secretion or antiinflammatory substances. These combinations may be administered either simultaneously or sequentially.

45

50

These compounds may be administered either on their own or in conjunction with other active substances by intravenous, subcutaneous, intramuscular, intrarectal, intraperitoneal or intranasal route, by inhalation or transdermally or orally, whilst aerosol formulations are particularly suitable for inhalation.

55

5

- 61 -

10

15

20

25

30

35

40

45

50

55

For pharmaceutical use the compounds according to the invention are generally used for warm-blooded vertebrates, particularly humans, in doses of 0.01-100 mg/kg of body weight, preferably 0.1-15 mg/kg. For administration they are formulated with one or more conventional inert carriers and/or diluents, e.g. with corn starch, lactose, glucose, microcrystalline cellulose, magnesium stearate, polyvinylpyrrolidone, citric acid, tartaric acid, water, water/ethanol, water/glycerol, water/sorbitol, water/polyethyleneglycol, propyleneglycol, stearylalcohol, carboxymethylcellulose or fatty substances such as hard fat or suitable mixtures thereof in conventional galenic preparations such as plain or coated tablets, capsules, powders, suspensions, solutions, sprays or suppositories.

The following Examples are intended to illustrate the present invention without restricting it:

5

- 62 -

Preparation of the starting compounds:

10

Example I

15

4-(3-chloro-4-fluorophenylamino)-6-[3-(4-tert.butyloxycarbonyl-piperazino)-propyloxy]-7-methoxy-quinazoline

20

500 mg of 4-(3-chloro-4-fluorophenylamino)-6-hydroxy-7-methoxy-quinazoline, 600 mg of 1-[3-(methanesulphonyloxy)propyl]-4-tert.butyloxycarbonyl-piperazine (prepared by reacting 1-(3-hydroxypropyl)-4-tert.butyloxycarbonyl-piperazine with methanesulphonic acid anhydride in the presence of triethylamine) and 520 mg of potassium carbonate are stirred in 20 ml of dimethylformamide for 8 hours at 80°C. A further 300 mg of the piperazino compound are added and stirring is continued for another 4 hours at 80°C. The reaction mixture is concentrated by evaporation and the residue is divided between water and ethyl acetate. The organic phase is concentrated by evaporation and the residue is purified by chromatography on a silica gel column with ethyl acetate.

25

Yield: 700 mg of (82 % of theory),

R_f value: 0.29 (silica gel; ethyl acetate/methanol = 9:1)

Mass spectrum: (M-H) = 544, 546

35

The following compounds are obtained analogously to Example I:

40

(1) 4-(3-chloro-4-fluorophenylamino)-6-[3-(1-tert.butyloxycarbonyl-4-piperidinyl)-propyloxy]-7-methoxy-quinazoline

R_f value: 0.70 (silica gel; ethyl acetate/methanol = 9:1)

45

(2) (S)-4-[(3-bromophenyl)amino]-6-{[1-(tert.butyloxycarbonyl)-pyrrolidine-2-yl]methoxy}-7-methoxy-quinazoline

melting point: 178°C

Mass spectrum (ESI⁺): m/z = 527, 529 [M-H]⁺

50

(3) (R)-4-[(3-bromophenyl)amino]-6-{[1-(tert.butyloxycarbonyl)-pyrrolidine-2-yl]methoxy}-7-methoxy-quinazoline

R_f value: 0.65 (silica gel, ethyl acetate/methanol = 9:1)

55

5

- 63 -

Mass spectrum (EI): m/z = 528, 530 [M]⁺

10

(4) (S)-4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[1-(tert.butyl-oxy-carbonyl)-pyrrolidin-2-yl]methoxy}-7-cyclopentyloxy-quinazoline

15

R_f value: 0.76 (silica gel, methylene chloride/methanol/concentrated aqueous ammonia = 90:10:0.1)

Mass spectrum (ESI⁺): m/z = 555, 557 [M-H]⁺

20

(5) (S)-4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[1-(tert.butyl-oxy-carbonyl)-pyrrolidin-2-yl]methoxy}-7-cyclopentylmethoxy-quinazoline

Melting point: 210-211.5°C

25

Mass spectrum (ESI⁺): m/z = 569, 571 [M-H]⁺

Example II

30

4-(3-chloro-4-fluorophenylamino)-6-[3-(1-piperazinyl)-propyloxy]-7-methoxy-quinazoline

35

600 mg of 4-(3-chloro-4-fluorophenylamino)-6-[3-(4-tert.butyl-oxy-carbonylpiperazino)propyloxy]-7-methoxy-quinazoline in 5 ml methylene chloride are mixed with 1.5 ml of trifluoroacetic acid and stirred for 2 hours at ambient temperature. The reaction mixture is concentrated by evaporation and combined with 2N NaOH. It is decanted off the sticky residue, the residue is taken up in methanol, concentrated by evaporation and triturated with diethyl ether.

40

Yield: 280 mg of (50 % of theory),

R_f value: 0.49 (aluminium oxide; ethyl acetate/methanol/conc. aqueous ammonia = 9:1:0.1)

45

Mass spectrum: (M+H)⁺ = 446, 448

The following compounds are obtained analogously to Example II:

50

(1) 4-(3-chloro-4-fluorophenylamino)-6-[3-(4-piperidinyl)propyloxy]-7-methoxy-quinazoline

55

5

- 64 -

R_f value: 0.33 (aluminium oxide; ethyl acetate/methanol/conc.
aqueous ammonia = 9:1:0.1)

10

Mass spectrum: $(M+H)^+ = 445, 447$

(2) (S)-4-[(3-bromophenyl)amino]-6-[(pyrrolidine-2-yl)methoxy]-

15

7-methoxy-quinazoline

melting point: 143°C

Mass spectrum (ESI⁺): $m/z = 429, 431 [M+H]^+$

(3) (R)-4-[(3-bromophenyl)amino]-6-[(pyrrolidine-2-yl)methoxy]-

20

7-methoxy-quinazoline

R_f value: 0.21 (silica gel, ethyl acetate/methanol/concentrated
aqueous ammonia solution = 9:1:0.1)

25

(4) (S)-4-[(3-chloro-4-fluoro-phenyl)amino]-6-[(pyrrolidin-
2-yl)methoxy]-7-cyclopentyloxy-quinazoline

R_f value: 0.18 (silica gel, methylene chloride/methanol/concen-
trated aqueous ammonia = 90:10:0.1)

30

Mass spectrum (ESI⁺): $m/z = 455, 457 [M-H]^+$

(5) (S)-4-[(3-chloro-4-fluoro-phenyl)amino]-6-[(pyrrolidin-
2-yl)methoxy]-7-cyclopentylmethoxy-quinazoline

35

R_f value: 0.36 (silica gel, methylene chloride/methanol/concen-
trated aqueous ammonia = 90:10:0.1)

Mass spectrum (ESI⁺): $m/z = 471, 473 [M+H]^+$

40

Example III

N-(3-Bromopropyl)sarcosine ethyl ester and N-(3-chloropropyl)-
sarcosine ethyl ester

45

6.9 ml of 1,3-dibromopropene in 20 ml acetonitrile are added
dropwise to 2.4 g of sarcosine ethyl ester hydrochloride and
6 ml of N-ethyl-diisopropylamine in 50 ml of acetonitrile.

50

After stirring overnight at ambient temperature the mixture is
concentrated by evaporation and the residue is divided between
ethyl acetate and water. The organic phase is concentrated by

55

5

- 65 -

evaporation and the residue is purified by chromatography on silica gel (ethyl acetate/methanol = 9:1).

10

Yield: 0.77 g,

R_f value: 0.80 (silica gel; ethyl acetate/methanol = 9:1)

Mass spectrum: M^+ = 237, 239 and 193, 195

15

The following compounds are obtained analogously to Example III:

(1) (S)-N-(3-Bromopropyl)proline methyl ester and

20

(S)-N-(3-chloropropyl)proline methyl ester

R_f value: 0.84 (silica gel, ethyl acetate/methanol = 9:1)

Mass spectrum (EI): m/z = 249, 251 $[M]^+$ and 205, 207 $[M]^+$

25

(2) (R)-N-(3-bromopropyl)proline methyl ester and

(R)-N-(3-chloropropyl)proline methyl ester

R_f value: 0.84 (silica gel, ethyl acetate/methanol = 9:1)

30

Mass spectrum (EI): m/z = 249, 251 $[M]^+$ and 205, 207 $[M]^+$

Example IV

35

4-[(3-bromophenyl)amino]-6-(2-bromethoxy)-7-methoxy-quinazoline

7.00 g of potassium carbonate and 8.70 ml of dibromoethane are added to 3.50 g of 4-[(3-bromophenyl)amino]-6-hydroxy-7-methoxy-quinazoline in 350 ml dimethylformamide. The reaction mixture is stirred for two hours at 85°C. Then the mixture is concentrated by evaporation and the oily residue is stirred with methanol. The bright yellow precipitate formed is suction filtered and dried.

40

Yield: 3.70 g (81 % of theory),

45

R_f value: 0.44 (silica gel, ethyl acetate)

Mass spectrum (ESI⁺): m/z = 452, 454, 456 $[M+H]^+$

The following compounds are obtained analogously to Example IV:

50

55

5

- 66 -

(1) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(2-bromo-ethoxy)-
7-cyclopentyloxy-quinazoline

10 R_f value: 0.74 (silica gel, methylene chloride/methanol/concentrated aqueous ammonia = 90:10:1)

Mass spectrum (ESI⁺): m/z = 478, 480, 482 [M-H]⁺

15 (2) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-cyclopentyloxy-
7-(2-bromo-ethoxy)-quinazoline

R_f value: 0.65 (silica gel, methylene chloride/methanol/concentrated aqueous ammonia = 90:10:0.1)

20 Mass spectrum (ESI⁺): m/z = 478, 480, 482 [M-H]⁺

Example V

25 4-[(3-bromophenyl)amino]-6-hydroxy-7-methoxy-quinazoline

34.50 g of 4-[(3-bromophenyl)amino]-6-methylcarbonyloxy-
7-methoxy-quinazoline in 350 ml ethanol are mixed with 35 ml of
40 40% sodium hydroxide solution. The reaction mixture is stirred
for three hours at ambient temperature. Then the mixture is
concentrated by evaporation, the residue is taken up in water
and neutralised with 2N hydrochloric acid. The precipitate
formed is suction filtered and dried overnight in the circu-
lating air drier at 50°C.

35 Yield: 28.30 g (92 % of theory),

melting point: 299°C

Mass spectrum (ESI⁺): m/z = 346, 348 [M+H]⁺

40

The following compounds are obtained analogously to Example V:

(1) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-benzyloxy-7-hydroxy-
45 quinazoline (The reaction is carried out with concentrated
aqueous ammonia in methanol.)

R_f value: 0.54 (silica gel, methylene chloride/methanol = 9:1)

Mass spectrum (ESI⁺): m/z = 396, 398 [M+H]⁺

50

55

5

- 67 -

10

(2) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-cyclopentyloxy-7-hydroxy-quinazoline (The reaction is carried out with concentrated, aqueous ammonia in methanol.)
R_f value: 0.53 (silica gel, methylene chloride/methanol/concentrated aqueous ammonia = 90:10:0.1)
Mass spectrum (ESI⁺): m/z = 374, 376 [M+H]⁺

15

Example VI

20

4-[(3-bromophenyl)amino]-6-methylcarbonyloxy-7-methoxy-quinazoline

25

13.0 ml of 3-bromoaniline are added to 30.00 g of 4-chloro-6-methylcarbonyloxy-7-methoxy-quinazoline in 600 ml isopropanol. The reaction mixture is refluxed for about four hours. The reaction mixture is then left to cool. The precipitate formed is suction filtered, washed thoroughly with cold isopropanol and dried.

30

Yield: 34.57 g (75 % of theory),
melting point: 238°C
Mass spectrum (ESI⁺): m/z = 388, 390 [M+H]⁺

The following compounds are obtained analogously to Example VI:

35

(1) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-benzyloxy-7-methylcarbonyloxy-quinazoline

Melting point: 267-268 °C

40

Mass spectrum (ESI⁺): m/z = 438, 440 [M+H]⁺

45

(2) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-cyclopentyloxy-7-methylcarbonyloxy-quinazoline

R_f value: 0.73 (silica gel, methylene chloride/methanol/concentrated aqueous ammonia = 90:10:0.1)

Mass spectrum (ESI⁺): m/z = 416, 418 [M+H]⁺

50

55

5

- 68 -

Example VII

10

4-[(3-bromophenyl)amino]-6-oxiranylmethoxy-7-methoxy-
quinazoline

15

1.50 ml of epibromohydrin are added to 5.00 g of
4-[(3-bromophenyl)amino]-6-hydroxy-7-methoxy-quinazoline and
4.75 g of potassium carbonate in 50 ml dimethylsulphoxide. The
reaction mixture is stirred for two days at 50°C. Then it is
diluted with about 150 ml of water and stirred for a further
two hours. The precipitate formed is suction filtered and
purified by chromatography on a silica gel column with ethyl
acetate as eluant.

20

Yield: 850 mg (15 % of theory),

melting point: 230-245°C

25

Mass spectrum (ESI⁺): m/z = 402, 404 [M+H]⁺

Example VIII

30

Dimethyl 2-(piperazin-1-yl)-succinate dihydrochloride

35

8.70 g of dimethyl 2-(4-benzyl-piperazin-1-yl)-succinate are
hydrogenated in a mixture of 100 ml methanol and 4.50 ml of
concentrated hydrochloric acid in the presence of 4.00 g of
palladium (10% on activated charcoal) at ambient temperature
until the calculated amount of hydrogen is taken up (about an
hour). Then the catalyst is removed by suction filtering and
the filtrate is concentrated by evaporation. A white gel-like
solid is left.

40

Yield: 4.18 g

R_f value: 0.80 (Reversed phase ready-made TLC plate (E. Merck),
acetonitrile/water/trifluoroacetic acid = 1:1:1)

45

Mass spectrum (ESI⁺): m/z = 231 [M+H]⁺

The following compound is obtained analogously to Example VIII:

50

(1) dimethyl 3-(piperazin-1-yl)-glutarate dihydrochloride

R_f value: 0.80 (Reversed phase ready-made TLC plate (E. Merck),
acetonitrile/water/trifluoroacetic acid = 1:1:1)

55

Mass spectrum (ESI⁺): m/z = 254 [M+H]⁺

Example IX

Dimethyl 2-(4-benzyl-piperazin-1-yl)-succinate

7.22 ml of dimethyl maleate are added to 10.0 ml of N-benzyl-piperazine in 15 ml dioxane. The reaction mixture is stirred for half an hour at ambient temperature. Then the mixture is refluxed for about a further three hours. For working up the reaction mixture is evaporated to dryness. An orange-yellow oil remains, which slowly crystallises.

Yield: 21.3 g (crude product),

R_f value: 0.85 (silica gel, methylene chloride/methanol/concentrated aqueous ammonia solution = 90:10:0.5)

Mass spectrum (EI): m/z = 320 [M]⁺

The following compound is obtained analogously to Example IX:

(1) dimethyl 3-(4-benzyl-piperazin-1-yl)-glutarate (reaction with dimethyl glutaconate)

R_f value: 0.49 (silica gel, cyclohexane/ethyl acetate = 1:1)

Mass spectrum (EI): m/z = 334 [M]⁺

Example X

4-[(3-Chloro-4-fluoro-phenyl)amino]-6-hydroxy-7-cyclopentyl-oxy-quinazoline

10 ml of trifluoroacetic acid are added to 1.95 g of 4-[(3-chloro-4-fluoro-phenyl)amino]-6-benzyloxy-7-cyclopentyl-oxy-quinazoline and the resulting dark brown solution is stirred at room temperature over night. Another 5 ml of trifluoroacetic acid are added and the mixture is stirred for approximately 2.5 hours at 50°C until the reaction is completed. The reaction mixture is concentrated in vacuo, diluted with water, and adjusted to pH 8-9 by addition of concentrated

aqueous ammonia. The precipitate is filtered off with suction, washed with water, and dried in vacuo at 60°C.

Yield: 1.45 g (92 % of theory),

R_f value: 0.56 (silica gel, methylene chloride/methanol 9:1)

Mass spectrum (ESI⁺): m/z = 372, 374 [M-H]⁺

The following compound is obtained analogously to Example X:

(1) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-hydroxy-7-cyclopentylmethoxy-quinazoline

R_f value: 0.73 (silica gel, methylene chloride/methanol/concentrated aqueous ammonia = 90:10:0.1)

Mass spectrum (ESI⁺): m/z = 386, 388 [M-H]⁺

Example XI

4-[(3-chloro-4-fluoro-phenyl)amino]-6-benzyloxy-7-cyclopentylmethoxy-quinazoline

0.65 ml of bromocyclopentane are added to a mixture of 2.30 g 4-[(3-chloro-4-fluoro-phenyl)amino]-6-benzyloxy-7-hydroxy-quinazoline and 6.00 g potassium carbonate in 6 ml of N,N-dimethyl-formamide and the reaction mixture is stirred for 18 hours at room temperature. Another 3.00 g of potassium carbonate and 4 drops of bromocyclopentane are added, and the resulting mixture is stirred for 2.5 hours at 50°C. The reaction mixture is partitioned between ethyl acetate and water, and the aqueous layer is extracted with ethyl acetate. The combined organic extracts are washed with concentrated aqueous sodium chloride solution, dried over magnesium sulfate and concentrated in vacuo. The oily residue is triturated with methanol, the resulting solid precipitate is filtered off, washed with cold methanol, and dried in vacuo.

Yield: 2.09 g (77 % of theory),

R_f value: 0.63 (silica gel, methylene chloride/methanol 9:1)

Mass spectrum (ESI⁺): m/z = 462, 464 [M-H]⁺

The following compound is obtained analogously to Example XI:

(1) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-benzyloxy-7-cyclopentylmethoxy-quinazoline

R_f value: 0.84 (silica gel, methylene chloride/methanol/concentrated aqueous ammonia = 90:10:1)

Mass spectrum (ESI⁺): m/z = 478, 480 [M+H]⁺

Example XII

4-chloro-6-benzyloxy-7-methylcarbonyloxy-quinazoline

Prepared by reaction of 6-benzyloxy-7-methylcarbonyloxy-3H-quinazolin-4-one with thionyl chloride in the presence of catalytic amounts of N,N-dimethyl-formamide.

Yield: 98 % of theory,

R_f value: 0.86 (silica gel, methylene chloride/methanol/concentrated aqueous ammonia = 90:10:0.1)

The following compound is obtained analogously to Example XII:

(1) 4-chloro-6-cyclopentylloxy-7-methylcarbonyloxy-quinazoline

R_f value: 0.69 (silica gel, methylene chloride/methanol/concentrated aqueous ammonia = 90:10:0.1)

Example XIII

6-benzyloxy-7-methylcarbonyloxy-3H-quinazolin-4-one

Prepared by reaction of 6-benzyloxy-7-hydroxy-3H-quinazolin-4-one with acetic anhydride in pyridine.

Yield: 68 % of theory,

Melting point: 231-233°C

Mass spectrum (ESI⁺): m/z = 309 [M-H]⁺

The following compound is obtained analogously to Example XIII:

(1) 6-cyclopentylloxy-7-methylcarbonyloxy-3H-quinazolin-4-one

5
10 R_f value: 0.57 (silica gel, methylene chloride/methanol/concentrated aqueous ammonia = 90:10:0.1)
Mass spectrum (ESI⁻): m/z = 287 [M-H]⁻

Example XIV

15 6-Benzylloxy-7-hydroxy-3H-quinazolin-4-one

Prepared by reaction of 2-amino-4-hydroxy-5-benzylloxy-benzoic acid with formamidine acetate in ethanol.

Yield: 72 % of theory,

20 R_f value: 0.45 (silica gel, methylene chloride/methanol/concentrated aqueous ammonia = 90:10:0.1)

Mass spectrum (ESI⁻): m/z = 267 [M-H]⁻

25 The following compound is obtained analogously to Example XIV:

(1) 6-cyclopentylloxy-7-hydroxy-3H-quinazolin-4-one

30 R_f value: 0.42 (silica gel, methylene chloride/methanol/concentrated aqueous ammonia = 90:10:0.1)

Mass spectrum (EI): m/z = 246 [M]⁺

Example XV

35 2-Amino-4-hydroxy-5-benzylloxy-benzoic acid

Prepared by catalytic hydrogenation of 2-nitro-4-hydroxy-5-benzylloxy-benzoic acid with Raney nickel in methanol.

40 Yield: 71 % of theory,

R_f value: 0.53 (silica gel, methylene chloride/methanol/concentrated aqueous ammonia = 90:10:0.1)

Mass spectrum (ESI⁻): m/z = 258 [M-H]⁻

45 The following compound is obtained analogously to Example XV:

(1) 2-amino-4-hydroxy-5-cyclopentylloxy-benzoic acid

50 R_f value: 0.38 (silica gel, methylene chloride/methanol/concentrated aqueous ammonia = 90:10:0.1)

Mass spectrum (ESI⁻): m/z = 236 [M-H]⁻

Example XVI2-Nitro-4-hydroxy-5-benzyloxy-benzoic acid

4.8 g of sodium are added portionwise to a mixture of 20.30 g 6-nitro-benzo[1,3]dioxole-5-carboxylic acid and 81.2 ml of benzyl alcohol in 120 ml of dimethyl sulfoxide cooled in an ice/water bath. The reaction mixture is allowed to warm up to room temperature and stirred for approximately 21 hours. The brownish red solution is diluted with 600 ml of water and extracted with methylene chloride. The aqueous layer is acidified with concentrated hydrochloric acid and stirred for two hours at room temperature. The precipitate is filtered off, washed with water, and dried.

Yield: 18.63g (67 % of theory),

Melting point: 172-175°C

Mass spectrum (ESI⁺): m/z = 288 [M-H]⁺

The following compound is obtained analogously to Example XVI:

(1) 2-nitro-4-hydroxy-5-cyclopentyloxy-benzoic acid

R_f value: 0.61 (silica gel, toluene/1,4-dioxane/ethanol/acetic acid = 90:10:10:6)

Mass spectrum (ESI⁺): m/z = 266 [M-H]⁺

Preparation of the end products:

Example 1

4-(3-chloro-4-fluorophenylamino)-6-{3-[4-(methoxycarbonylmethyl)-1-piperazinyl]propyloxy}-7-methoxy-quinazoline

0.07 ml of methyl bromoacetate in 1 ml of acetonitrile is added dropwise to 250 mg of 4-(3-chloro-4-fluorophenylamino)-6-[3-(1-piperazinyl)propyloxy]-7-methoxy-quinazoline and 0.13 ml N-ethyl-diisopropylamine in 5 ml of acetonitrile. After 2 hours' stirring at ambient temperature the mixture is concentrated by evaporation, mixed with water and extracted with ethyl acetate. The organic phases are washed with saline solution, then dried with magnesium sulphate and concentrated by evaporation.

Yield: 150 mg (51 % of theory),

R_f value: 0.54 (silica gel; ethyl acetate/methanol/conc.

aqueous ammonia = 9:1:0.1)

Mass spectrum: (M-H) = 516, 518

The following compounds are obtained analogously to Example 1:

(1) 4-(3-chloro-4-fluorophenylamino)-6-{3-[1-(methoxycarbonylmethyl)-4-piperidinyl]propyloxy}-7-methoxy-quinazoline

R_f value: 0.79 (silica gel; ethyl acetate/methanol/conc.

aqueous ammonia = 9:1:0.1)

Mass spectrum: M^+ = 516, 518

(2) (S)-4-[(3-bromophenyl)amino]-6-({1-[(ethoxycarbonyl)methyl]-pyrrolidin-2-yl}methoxy)-7-methoxy-quinazoline

R_f value: 0.68 (silica gel, ethyl acetate/methanol/concentrated

aqueous ammonia solution = 9:1:0.1)

Mass spectrum (EI): m/z = 514, 516 [M]⁺

(3) (R)-4-[(3-bromophenyl)amino]-6-({1-[(ethoxycarbonyl)methyl]-pyrrolidin-2-yl}methoxy)-7-methoxy-quinazoline

R_f value: 0.75 (silica gel, ethyl acetate/methanol = 9:1)

Mass spectrum (EI): m/z = 514, 516 [M]⁺

(4) (S)-4-[(3-chloro-4-fluoro-phenyl)amino]-6-({1-(methoxy-carbonyl)methyl}-pyrrolidin-2-yl)methoxy)-7-cyclopentyloxy-quinazoline

R_f value: 0.59 (silica gel, methylene chloride/methanol/concentrated aqueous ammonia = 90:10:0.1)

Mass spectrum (ESI⁺): m/z = 527, 529 [M-H]⁺

(5) (S)-4-[(3-chloro-4-fluoro-phenyl)amino]-6-({1-(methoxy-carbonyl)methyl}-pyrrolidin-2-yl)methoxy)-7-cyclopentyl-methoxy-quinazoline

R_f value: 0.67 (silica gel, methylene chloride/methanol/concentrated aqueous ammonia = 90:10:0.1)

Mass spectrum (ESI⁺): m/z = 541, 543 [M-H]⁺

Example 2

4-(3-chloro-4-fluorophenylamino)-6-{3-[N-(ethoxycarbonylmethyl)-N-methylaminolpropyloxy]}-7-methoxy-quinazoline

380 mg of a mixture of N-(3-bromopropyl)sarcosine ethyl ester and N-(3-chloropropyl)sarcosine ethyl ester in 5 ml dimethylformamide are added dropwise to 500 mg of 4-(3-chloro-4-fluorophenylamino)-6-hydroxy-7-methoxy-quinazoline and 220 mg of potassium tert.butoxide in 15 ml dimethylformamide. After 3 hours' stirring at 80°C and standing overnight a further 110 mg of potassium tert.butoxide and 190 mg of the sarcosine mixture are added and the reaction mixture is stirred for 4 hours at 80°C. It is filtered, the filtrate is concentrated by evaporation, the residue is taken up in water and extracted with ethyl acetate. The organic phase is separated off, dried and concentrated by evaporation. The residue is purified by chromatography on a silica gel column.

Yield: 390 mg of (52 % of theory),

R_f value: 0.68 (silica gel; ethyl acetate/methanol/conc. aqueous ammonia = 9:1:0.1)

Mass spectrum: (M-H) = 475, 477

5

The following compounds are obtained analogously to Example 2:

10

(1) (S)-4-[(3-bromophenyl)amino]-6-[3-(2-methoxycarbonyl-pyrrolidin-1-yl)propyloxy]-7-methoxy-quinazoline

R_f value: 0.38 (silica gel, ethyl acetate/methanol = 9:1)

Mass spectrum (EI): m/z = 514, 516 [M]⁺

15

(2) (R)-4-[(3-bromophenyl)amino]-6-[3-(2-methoxycarbonyl-pyrrolidin-1-yl)propyloxy]-7-methoxy-quinazoline

R_f value: 0.41 (silica gel, ethyl acetate/methanol = 9:1)

20

Mass spectrum (EI): m/z = 514, 516 [M]⁺

Example 3

25

4-[(3-bromophenyl)amino]-6-(2-{4-[(ethoxycarbonyl)methyl]-piperazin-1-yl}ethoxy)-7-methoxy-quinazoline

30

1.50 ml of diisopropyl-ethylamine and 1.10 ml of 1-[(ethoxycarbonyl)methyl]-piperazine are added to 1.00 g of 4-[(3-bromophenyl)amino]-6-(2-bromoethoxy)-7-methoxy-quinazoline in 20 ml acetonitrile. The reaction mixture is stirred for two days at ambient temperature. The precipitate formed is filtered off and the filtrate is concentrated by evaporation. The residue is taken up in ethyl acetate and washed once with saturated sodium hydrogen carbonate solution and once with water. The organic phase is dried over magnesium sulphate and concentrated by evaporation. The crude product is purified on a silica gel column with ethyl acetate/ethanol/concentrated aqueous ammonia solution (9:1:0.1) as eluant.

40

Yield: 450 mg of (38 % of theory),

melting point: 155°C

45

Mass spectrum (EI): m/z = 543, 545 [M]⁺

The following compounds are obtained analogously to Example 3:

50

(1) 4-[(3-bromophenyl)amino]-6-(2-{N-[(ethoxycarbonyl)methyl]-N-methylamino}ethoxy)-7-methoxy-quinazoline

R_f value: 0.55 (silica gel, ethyl acetate/methanol = 9:1)

55

5

Mass spectrum (EI): $m/z = 488, 490$ [M]⁺

10

(2) 4-[(3-bromophenyl)amino]-6-(2-{N,N-bis[(ethoxycarbonyl)methyl]amino}ethoxy)-7-methoxy-quinazoline

R_f value: 0.38 (silica gel, ethyl acetate)

Mass spectrum (EI): $m/z = 560, 562$ [M]⁺

15

(3) 4-[(3-bromophenyl)amino]-6-(2-{4-[1,2 bis(methoxycarbonyl)-ethyl]-piperazin-1-yl}ethoxy)-7-methoxy-quinazoline

R_f value: 0.61 (silica gel, ethyl acetate/methanol = 9:1)

Mass spectrum (EI): $m/z = 601, 603$ [M]⁺

20

(4) 4-[(3-bromophenyl)amino]-6-[2-(4-{1-[(methoxycarbonyl)methyl]-2-(methoxycarbonyl)-ethyl}-piperazin-1-yl)ethoxy]-7-methoxy-quinazoline

R_f value: 0.51 (silica gel, ethyl acetate/methanol = 9:1)

Mass spectrum (ESI⁺): $m/z = 616, 618$ [M+H]⁺

25

(5) (R)-4-[(3-chloro-4-fluoro-phenyl)amino]-6-{2-[2-(methoxycarbonyl)-pyrrolidin-1-yl]-ethoxy}-7-cyclopentyloxy-quinazoline

R_f value: 0.65 (silica gel, methylene chloride/methanol/concentrated aqueous ammonia = 90:10:0.1)

Mass spectrum (ESI⁺): $m/z = 527, 529$ [M-H]⁺

30

(6) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(2-{4-[(ethoxycarbonyl)methyl]-piperazin-1-yl}-ethoxy)-7-cyclopentyloxy-quinazoline

R_f value: 0.54 (silica gel, methylene chloride/methanol/concentrated aqueous ammonia = 90:10:0.1)

Mass spectrum (ESI⁺): $m/z = 570, 572$ [M-H]⁺

40

(7) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-cyclopentyloxy-7-(2-{N-(2-hydroxy-2-methyl-prop-1-yl)-N-[(ethoxycarbonyl)methyl]-amino}-ethoxy)-quinazoline

R_f value: 0.28 (silica gel, ethyl acetate)

Mass spectrum (ESI⁺): $m/z = 573, 575$ [M-H]⁺

50

55

(8) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-cyclopentyloxy-
7-[2-(6,6-dimethyl-2-oxo-morpholin-4-yl)-ethoxy]-quinazoline
(This compound was obtained by treatment of the compound prepared by example 3(7) with toluene-4-sulfonic acid in toluene.)

R_f value: 0.23 (silica gel, ethyl acetate)

Mass spectrum (ESI⁺): m/z = 527, 529 [M-H]⁺

(9) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-cyclopentyloxy-
7-[2-[N-(2-oxo-tetrahydrofuran-3-yl)-N-methyl-amino]-ethoxy]-
quinazoline (The starting material 3-methylamino-dihydro-furan-2-one was prepared by reaction of 3-bromo-dihydro-furan-2-one with N-methylbenzylamine and subsequent hydrogenolytic removal of the benzyl group)

R_f value: 0.42 (silica gel, ethyl acetate/methanol = 9:1)

Mass spectrum (ESI⁺): m/z = 515, 517 [M+H]⁺

(10) 4-[(3-bromo-phenyl)amino]-6-(2-{N-(2-hydroxy-2-methyl-prop-1-yl)-N-[(ethoxycarbonyl)methyl]-amino}-ethoxy)-7-methoxy-quinazoline

(11) 4-[(3-bromo-phenyl)amino]-6-[2-(6,6-dimethyl-2-oxo-morpholin-4-yl)-ethoxy]-7-methoxy-quinazoline

R_f value: 0.33 (silica gel, ethyl acetate)

Mass spectrum (ESI⁺): m/z = 499, 500 [M+H]⁺

(12) 4-[(3-bromo-phenyl)amino]-6-[2-[N-(2-oxo-tetrahydrofuran-4-yl)-N-methyl-amino]-ethoxy]-7-methoxy-quinazoline (The starting material 4-methylamino-dihydro-furan-2-one was prepared by reaction of 5H-furan-2-one with N-methyl-benzylamine and subsequent hydrogenolytic removal of the benzyl group)

R_f value: 0.38 (silica gel, ethyl acetate/methanol = 9:1)

Mass spectrum (ESI⁺): m/z = 485, 487 [M-H]⁺

Example 4

4-[(3-bromophenyl)amino]-6-(3-{4-[(ethoxycarbonyl)methyl]-
piperazin-1-yl}-2-hydroxy-propyloxy)-7-methoxy-quinazoline
0.16 ml of 1-[(ethoxycarbonyl)methyl]-piperazine are added to
500 mg of 4-[(3-bromophenyl)amino]-6-oxiranylmethoxy-7-methoxy-
quinazoline in 5 ml ethanol. The reaction mixture is refluxed
for about 6 hours. Then the mixture is concentrated by evapora-
tion and the crude product is purified by chromatography on a
silica gel column with ethyl acetate/ethanol/concentrated
aqueous ammonia solution (9:1:0.1) as eluant.
Yield: 97 mg of (14 % of theory),
melting point: 118-122°C
Mass spectrum (EI): m/z = 573, 575 [M]⁺

Example 5

4-[(3-bromophenyl)amino]-6-{2-[4-(carboxymethyl)-piperazin-
1-yl]ethoxy}-7-methoxy-quinazoline
0.19 ml of 1N sodium hydroxide solution are added to 100 mg of
4-[(3-bromophenyl)amino]-6-(2-{4-[(ethoxycarbonyl)methyl]-
piperazin-1-yl}ethoxy)-7-methoxy-quinazoline in 0.30 ml of
tetrahydrofuran. The reaction mixture is stirred for three
hours at ambient temperature. Another 0.9 ml of 1N sodium
hydroxide solution are added and the mixture is stirred
overnight. Then it is neutralised with 1N hydrochloric acid and
concentrated by evaporation. The solid residue is triturated
with ethyl acetate and suction filtered.
Yield: 100 mg (contains about 0.5 equivalents sodium chloride),
R_f value: 0.50 (Reversed phase ready-made TLC plate (E. Merck),
acetonitrile/water/trifluoroacetic acid = 50:50:1)
Mass spectrum (ESI⁺): m/z = 514, 516 [M-H]⁺

The following compounds may also be obtained analogously to the
foregoing Examples and other methods known from the literature:

- (1) 4-[(3-bromophenyl)amino]-6-({1-[(methoxycarbonyl)methyl]-piperidin-4-yl}methoxy)-7-methoxy-quinazoline
- (2) 4-[(3-methylphenyl)amino]-6-({1-[(ethoxycarbonyl)methyl]-piperidin-4-yl}methoxy)-7-methoxy-quinazoline
- (3) 4-[(3-chlorophenyl)amino]-6-({1-[(ethoxycarbonyl)methyl]-piperidin-4-yl}methoxy)-7-methoxy-quinazoline
- (4) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-({1-[(ethoxycarbonyl)methyl]-piperidin-4-yl}methoxy)-7-methoxy-quinazoline
- (5) 4-[(indol-5-yl)amino]-6-({1-[(ethoxycarbonyl)methyl]-piperidin-4-yl}methoxy)-7-methoxy-quinazoline
- (6) 4-[(1-phenylethyl)amino]-6-({1-[(ethoxycarbonyl)methyl]-piperidin-4-yl}methoxy)-7-methoxy-quinazoline
- (7) 4-[(3-ethynylphenyl)amino]-6-({1-[(ethoxycarbonyl)methyl]-piperidin-4-yl}methoxy)-7-methoxy-quinazoline
- (8) 4-[(3-bromophenyl)amino]-6-({1-[(ethoxycarbonyl)methyl]-piperidin-4-yl}methoxy)-7-methoxy-quinazoline
- (9) 4-[(3-bromophenyl)amino]-6-({1-[(hexyloxycarbonyl)methyl]-piperidin-4-yl}methoxy)-7-methoxy-quinazoline
- (10) 4-[(3-bromophenyl)amino]-6-({1-[2-(ethoxycarbonyl)ethyl]-piperidin-4-yl}methoxy)-7-methoxy-quinazoline
- (11) 4-[(3-bromophenyl)amino]-6-({1-[3-(ethoxycarbonyl)propyl]-piperidin-4-yl}methoxy)-7-methoxy-quinazoline
- (12) 4-[(3-bromophenyl)amino]-6-({1-[(ethoxycarbonyl)methyl]-piperidin-3-yl}methoxy)-7-methoxy-quinazoline

5

- 81 -

(13) 4-[(3-bromophenyl)amino]-6-({1-[(ethoxycarbonyl)methyl]-pyrrolidin-2-yl}methoxy)-7-methoxy-quinazoline

10

(14) 4-[(3-bromophenyl)amino]-6-({1-[(dimethoxyphosphoryl)methyl]-piperidin-4-yl}methoxy)-7-methoxy-quinazoline

15

(15) 4-[(3-bromophenyl)amino]-6-({1-[(methoxy)(methyl)phosphoryl]methyl}-piperidin-4-yl}methoxy)-7-methoxy-quinazoline

20

(16) 4-[(3-bromophenyl)amino]-6-({1-[1,2-bis(ethoxycarbonyl)ethyl]-piperidin-4-yl}methoxy)-7-methoxy-quinazoline

25

(17) 4-[(3-bromophenyl)amino]-6-({1-({1-[(ethoxycarbonyl)methyl]-2-(ethoxycarbonyl)-ethyl}-piperidin-4-yl}methoxy)-7-methoxy-quinazoline

30

(18) 4-[(3-bromophenyl)amino]-6-(2-{1-[1-(methoxycarbonyl)-ethyl]-piperidin-4-yl}ethoxy)-7-methoxy-quinazoline

35

(19) 4-[(3-bromophenyl)amino]-6-(2-{1-[(methoxycarbonyl)methyl]-piperidin-4-yl}ethoxy)-7-methoxy-quinazoline

40

(20) 4-[(3-bromophenyl)amino]-6-(2-{4-[(methoxycarbonyl)methyl]-piperazin-1-yl}ethoxy)-7-methoxy-quinazoline

45

(21) 4-[(3-bromophenyl)amino]-6-(2-{4-[(ethoxycarbonyl)methyl]-piperidin-4-yl}ethoxy)-7-methoxy-quinazoline

50

(22) 4-[(3-bromophenyl)amino]-6-(2-{1-[1,2-bis(ethoxycarbonyl)ethyl]-piperidin-4-yl}ethoxy)-7-methoxy-quinazoline

55

(23) 4-[(3-bromophenyl)amino]-6-(2-{4-[1,2-bis(ethoxycarbonyl)ethyl]-piperazin-1-yl}ethoxy)-7-methoxy-quinazoline

(25) 4-[(3-bromophenyl)amino]-6-[2-(4-{1-[(ethoxycarbonyl)methyl]-2-(ethoxycarbonyl)-ethyl}-piperazin-1-yl)ethoxy]-7-methoxy-quinazoline

(26) 4-[(3-bromophenyl)amino]-6-[2-(1-{1-[(ethoxycarbonyl)methyl]-2-(ethoxycarbonyl)-ethyl}-piperidin-4-yl)ethoxy]-7-methoxy-quinazoline

(27) 4-[(3-bromophenyl)amino]-6-{2-[2-(methoxycarbonyl)-pyrrolidin-1-yl]ethoxy}-7-methoxy-quinazoline

(28) 4-[(3-bromophenyl)amino]-6-{2-[2-(ethoxycarbonyl)-piperidin-1-yl]ethoxy}-7-methoxy-quinazoline

(29) 4-[(3-bromophenyl)amino]-6-(3-{1-[(methoxycarbonyl)methyl]-piperidin-4-yl}propyloxy)-7-methoxy-quinazoline

(30) 4-[(3-bromophenyl)amino]-6-(3-{4-[(methoxycarbonyl)methyl]-piperazin-1-yl}propyloxy)-7-methoxy-quinazoline

(31) 4-[(3-bromophenyl)amino]-6-(3-{4-[(ethoxycarbonyl)methyl]-piperazin-1-yl}propyloxy)-7-methoxy-quinazoline

(32) 4-[(3-bromophenyl)amino]-6-(3-{1-[(ethoxycarbonyl)methyl]-piperidin-4-yl}propyloxy)-7-methoxy-quinazoline

(33) 4-[(3-bromophenyl)amino]-6-(3-{1-[(ethoxycarbonyl)methyl]-piperidin-4-yl}-2-hydroxy-propyloxy)-7-methoxy-quinazoline

(34) 4-[(3-bromophenyl)amino]-6-(3-{4-[(ethoxycarbonyl)methyl]-piperazin-1-yl}-2-hydroxy-propyloxy)-7-methoxy-quinazoline

(35) 4-[(3-methylphenyl)amino]-6-(3-{4-[(ethoxycarbonyl)methyl]-piperazin-1-yl}propyloxy)-7-methoxy-quinazoline

(36) 4-[(3-chlorophenyl)amino]-6-(3-{4-[(ethoxycarbonyl)methyl]-piperazin-1-yl}propyloxy)-7-methoxy-quinazoline

5

10

(37) 4-[(indol-5-yl)amino]-6-(3-{4-[(ethoxycarbonyl)methyl]-piperazin-1-yl}propyloxy)-7-methoxy-quinazoline

15

(38) 4-[(1-phenylethyl)amino]-6-(3-{4-[(ethoxycarbonyl)methyl]-piperazin-1-yl}propyloxy)-7-methoxy-quinazoline

20

(39) 4-[(3-bromophenyl)amino]-6-{3-[2-(methoxycarbonyl)-pyrrolidin-1-yl]propyloxy}-7-methoxy-quinazoline

25

(40) 4-[(3-bromophenyl)amino]-6-{3-[3-(methoxycarbonyl)-4-methyl-piperazin-1-yl]propyloxy}-7-methoxy-quinazoline

30

(41) 4-[(3-bromophenyl)amino]-6-({1-[(ethoxycarbonyl)methyl]-piperidin-4-yl}methoxy)-7-ethoxy-quinazoline

35

(42) 4-[(3-bromophenyl)amino]-6-({1-[(ethoxycarbonyl)methyl]-piperidin-4-yl}methoxy)-7-(2-methoxyethoxy)-quinazoline

40

(43) 4-[(3-bromophenyl)amino]-6-(2-{1-[(ethoxycarbonyl)methyl]-piperidin-4-yl}ethoxy)-7-(2-methoxyethoxy)-quinazoline

45

(44) 4-[(3-bromophenyl)amino]-6-(2-{4-[(ethoxycarbonyl)methyl]-piperazin-1-yl}ethoxy)-7-(2-methoxyethoxy)-quinazoline

50

(45) 4-[(3-bromophenyl)amino]-6-(2-{4-[(ethoxycarbonyl)methyl]-piperazin-1-yl}ethoxy)-7-ethoxy-quinazoline

(46) 4-[(3-bromophenyl)amino]-6-(3-{1-[(ethoxycarbonyl)methyl]-piperidin-4-yl}propyloxy)-7-ethoxy-quinazoline

(47) 4-[(3-bromophenyl)amino]-6-(3-{4-[(ethoxycarbonyl)methyl]-piperazin-1-yl}propyloxy)-7-(2-methoxyethoxy)-quinazoline

(48) 4-[(3-bromophenyl)amino]-6-(3-{1-[(dimethoxyphosphoryl)-methyl]-piperidin-4-yl}propyloxy)-7-methoxy-quinazoline

55

(49) 4-[(3-bromophenyl)amino]-6-(3-{4-[(dimethoxyphosphoryl)-methyl]-piperazin-1-yl}propyloxy)-7-methoxy-quinazoline

(50) 4-[(3-bromophenyl)amino]-6-[3-(4-{[(methoxy)(ethyl)phosphoryl]methyl}-piperazin-1-yl)propyloxy]-7-methoxy-quinazoline

(51) 4-[(3-bromophenyl)amino]-6-[3-(1-{[(methoxy)(ethyl)phosphoryl]methyl}-piperidin-4-yl)propyloxy]-7-methoxy-quinazoline

(52) 4-[(3-bromophenyl)amino]-6-(3-{4-[1,2-bis(ethoxycarbonyl)-ethyl]-piperazin-1-yl}propyloxy)-7-methoxy-quinazoline

(53) 4-[(3-bromophenyl)amino]-6-[3-(1-{1-[(ethoxycarbonyl)methyl]-2-(ethoxycarbonyl)-ethyl}-piperidin-4-yl)propyloxy]-7-methoxy-quinazoline

(54) 4-[(3-bromophenyl)amino]-6-(4-{1-[(ethoxycarbonyl)methyl]-piperidin-4-yl}butyloxy)-7-methoxy-quinazoline

(55) 4-[(3-bromophenyl)amino]-6-(4-{4-[(ethoxycarbonyl)methyl]-piperazin-1-yl}butyloxy)-7-methoxy-quinazoline

(56) 4-[(3-bromophenyl)amino]-6-(2-{N-[(ethoxycarbonyl)methyl]-N-methylamino}ethoxy)-7-methoxy-quinazoline

(57) 4-[(3-bromophenyl)amino]-6-(2-{N,N-bis[(ethoxycarbonyl)methyl]amino}ethoxy)-7-methoxy-quinazoline

(58) 4-[(3-bromophenyl)amino]-6-(2-{N-[(ethoxycarbonyl)methyl]-N-ethylamino}ethoxy)-7-methoxy-quinazoline

(59) 4-[(3-bromophenyl)amino]-6-(2-{N-[(ethoxycarbonyl)methyl]-N-(cyclopropylmethyl)-amino}ethoxy)-7-methoxy-quinazoline

(60) 4-[(3-bromophenyl)amino]-6-(2-{[(ethoxycarbonyl)methyl]-amino}ethoxy)-7-methoxy-quinazoline

(61) 4-[(3-bromophenyl) amino]-6-(2-{N-[(ethoxycarbonyl)methyl]-N-cyclopropyl-amino}ethoxy)-7-methoxy-quinazoline

(62) 4-[(3-bromophenyl) amino]-6-(2-{N-[(methoxycarbonyl)methyl]-N-methylamino}ethoxy)-7-methoxy-quinazoline

(63) 4-[(3-bromophenyl) amino]-6-(3-{N-[(methoxycarbonyl)methyl]-N-methylamino}propyloxy)-7-methoxy-quinazoline

(64) 4-[(3-bromophenyl) amino]-6-(3-{N,N-bis[(methoxycarbonyl)methyl]amino}propyloxy)-7-methoxy-quinazoline

(65) 4-[(3-bromophenyl) amino]-6-(3-{[(ethoxycarbonyl)methyl]-amino}propyloxy)-7-methoxy-quinazoline

(66) 4-[(3-bromophenyl) amino]-6-(4-{N-[(ethoxycarbonyl)methyl]-N-methylamino}butyloxy)-7-methoxy-quinazoline

(67) 4-[(3-bromophenyl) amino]-6-(4-{N,N-bis[(ethoxycarbonyl)methyl]amino}butyloxy)-7-methoxy-quinazoline

(68) 4-[(3-bromophenyl) amino]-6-({4-[(methoxycarbonyl)methyl]-2-oxo-morpholin-6-yl}methyloxy)-7-methoxy-quinazoline

(69) 4-[(3-bromophenyl) amino]-6-[(4-methyl-2-oxo-morpholin-6-yl)methyloxy]-7-methoxy-quinazoline

(70) 4-[(3-bromophenyl) amino]-6-[(2-oxo-morpholin-6-yl)methyloxy]-7-methoxy-quinazoline

(71) 4-[(4-amino-3,5-dibromo-phenyl) amino]-6-(3-{4-[(methoxycarbonyl)methyl]-piperazin-1-yl}propyloxy)-7-methoxy-quinazoline

(72) 4-[(4-amino-3,5-dibromo-phenyl) amino]-6-(3-{1-[(methoxycarbonyl)methyl]-piperidin-4-yl}propyloxy)-7-methoxy-quinazoline

5

10

(73) 4-[(3-bromophenyl)amino]-6,7-bis(2-{N-[(ethoxycarbonyl)methyl]-N-methylamino}ethoxy)-quinazoline

15

(74) 4-[(3-bromophenyl)amino]-6,7-bis(3-{N-[(ethoxycarbonyl)methyl]-N-methylamino}propyloxy)-quinazoline

20

(75) 4-[(3-bromophenyl)amino]-6-[3-(morpholino)propyloxy]-7-[(ethoxycarbonyl)methoxy]-quinazoline

(76) 4-[(3-bromophenyl)amino]-6-[2-(morpholino)ethoxy]-7-[(ethoxycarbonyl)methoxy]-quinazoline

25

(77) 4-[(3-bromophenyl)amino]-7-({1-[(methoxycarbonyl)methyl]-piperidin-4-yl}methoxy)-6-methoxy-quinazoline

(78) 4-[(3-methylphenyl)amino]-7-({1-[(ethoxycarbonyl)methyl]-piperidin-4-yl}methoxy)-6-methoxy-quinazoline

30

(79) 4-[(3-chlorophenyl)amino]-7-({1-[(ethoxycarbonyl)methyl]-piperidin-4-yl}methoxy)-6-methoxy-quinazoline

35

(80) 4-[(3-chloro-4-fluoro-phenyl)amino]-7-({1-[(ethoxycarbonyl)methyl]-piperidin-4-yl}methoxy)-6-methoxy-quinazoline

40

(81) 4-[(indol-5-yl)amino]-7-({1-[(ethoxycarbonyl)methyl]-piperidin-4-yl}methoxy)-6-methoxy-quinazoline

(82) 4-[(1-phenylethyl)amino]-7-({1-[(ethoxycarbonyl)methyl]-piperidin-4-yl}methoxy)-6-methoxy-quinazoline

45

(83) 4-[(3-ethynylphenyl)amino]-7-({1-[(ethoxycarbonyl)methyl]-piperidin-4-yl}methoxy)-6-methoxy-quinazoline

50

(84) 4-[(3-bromophenyl)amino]-7-({1-[(ethoxycarbonyl)methyl]-piperidin-4-yl}methoxy)-6-methoxy-quinazoline

55

(85) 4-[(3-bromophenyl)amino]-7-({1-[(hexyloxycarbonyl)methyl]-piperidin-4-yl}methoxy)-6-methoxy-quinazoline

(86) 4-[(3-bromophenyl)amino]-7-({1-[2-(ethoxycarbonyl)ethyl]-piperidin-4-yl}methoxy)-6-methoxy-quinazoline

(87) 4-[(3-bromophenyl)amino]-7-({1-[3-(ethoxycarbonyl)propyl]-piperidin-4-yl}methoxy)-6-methoxy-quinazoline

(88) 4-[(3-bromophenyl)amino]-7-({1-[(ethoxycarbonyl)methyl]-piperidin-3-yl}methoxy)-6-methoxy-quinazoline

(89) 4-[(3-bromophenyl)amino]-7-({1-[(ethoxycarbonyl)methyl]-pyrrolidin-2-yl}methoxy)-6-methoxy-quinazoline

(90) 4-[(3-bromophenyl)amino]-7-({1-[(dimethoxyphosphoryl)methyl]-piperidin-4-yl}methoxy)-6-methoxy-quinazoline

(91) 4-[(3-bromophenyl)amino]-7-({1-[(methoxy)(methyl)phosphoryl)methyl]-piperidin-4-yl}methoxy)-6-methoxy-quinazoline

(92) 4-[(3-bromophenyl)amino]-7-({1-[1,2-bis(ethoxycarbonyl)ethyl]-piperidin-4-yl}methoxy)-6-methoxy-quinazoline

(93) 4-[(3-bromophenyl)amino]-7-({1-[1-[(ethoxycarbonyl)methyl]-2-(ethoxycarbonyl)-ethyl]-piperidin-4-yl}methoxy)-6-methoxy-quinazoline

(94) 4-[(3-bromophenyl)amino]-7-(2-[1-[1-(methoxycarbonyl)-ethyl]-piperidin-4-yl]ethoxy)-6-methoxy-quinazoline

(95) 4-[(3-bromophenyl)amino]-7-(2-[1-[(methoxycarbonyl)methyl]-piperidin-4-yl]ethoxy)-6-methoxy-quinazoline

(96) 4-[(3-bromophenyl)amino]-7-(2-[4-[(methoxycarbonyl)methyl]-piperazin-1-yl]ethoxy)-6-methoxy-quinazoline

5

(97) 4-[(3-bromophenyl)amino]-7-(2-{4-[(ethoxycarbonyl)methyl]-piperazin-1-yl}ethoxy)-6-methoxy-quinazoline

10

(98) 4-[(3-bromophenyl)amino]-7-(2-{1-[(ethoxycarbonyl)methyl]-piperidin-4-yl}ethoxy)-6-methoxy-quinazoline

15

(99) 4-[(3-bromophenyl)amino]-7-(2-{1-[1,2-bis(ethoxycarbonyl)ethyl]-piperidin-4-yl}ethoxy)-6-methoxy-quinazoline

20

(100) 4-[(3-bromophenyl)amino]-7-(2-{4-[1,2-bis(ethoxycarbonyl)ethyl]-piperazin-1-yl}ethoxy)-6-methoxy-quinazoline

25

(101) 4-[(3-bromophenyl)amino]-7-[2-(4-{1-[(ethoxycarbonyl)methyl]-2-(ethoxycarbonyl)-ethyl}-piperazin-1-yl)ethoxy]-6-methoxy-quinazoline

30

(102) 4-[(3-bromophenyl)amino]-7-[2-(1-{1-[(ethoxycarbonyl)methyl]-2-(ethoxycarbonyl)-ethyl}-piperidin-4-yl)ethoxy]-6-methoxy-quinazoline

35

(103) 4-[(3-bromophenyl)amino]-7-{2-[2-(methoxycarbonyl)-pyrrolidin-1-yl]ethoxy}-6-methoxy-quinazoline

40

(104) 4-[(3-bromophenyl)amino]-7-{2-[2-(ethoxycarbonyl)-piperidin-1-yl]ethoxy}-6-methoxy-quinazoline

45

(105) 4-[(3-bromophenyl)amino]-7-(3-{1-[(methoxycarbonyl)methyl]-piperidin-4-yl}propyloxy)-6-methoxy-quinazoline

(106) 4-[(3-bromophenyl)amino]-7-(3-{4-[(methoxycarbonyl)methyl]-piperazin-1-yl}propyloxy)-6-methoxy-quinazoline

50

(107) 4-[(3-bromophenyl)amino]-7-(3-{4-[(ethoxycarbonyl)methyl]-piperazin-1-yl}propyloxy)-6-methoxy-quinazoline

55

(108) 4-[(3-bromophenyl)amino]-7-(3-{1-[(ethoxycarbonyl)methyl]-piperidin-4-yl}propyloxy)-6-methoxy-quinazoline

5
10 (109) 4-[(3-bromophenyl)amino]-7-(3-{1-[(ethoxycarbonyl)methyl]-piperidin-4-yl}-2-hydroxy-propyloxy)-6-methoxy-quinazoline

15 (110) 4-[(3-bromophenyl)amino]-7-(3-{4-[(ethoxycarbonyl)methyl]-piperazin-1-yl}-2-hydroxy-propyloxy)-6-methoxy-quinazoline

20 (111) 4-[(3-methylphenyl)amino]-7-(3-{4-[(ethoxycarbonyl)methyl]-piperazin-1-yl}propyloxy)-6-methoxy-quinazoline

(112) 4-[(3-chlorophenyl)amino]-7-(3-{4-[(ethoxycarbonyl)methyl]-piperazin-1-yl}propyloxy)-6-methoxy-quinazoline

25 (113) 4-[(indol-5-yl)amino]-7-(3-{4-[(ethoxycarbonyl)methyl]-piperazin-1-yl}propyloxy)-6-methoxy-quinazoline

30 (114) 4-[(1-phenylethyl)amino]-7-(3-{4-[(ethoxycarbonyl)methyl]-piperazin-1-yl}propyloxy)-6-methoxy-quinazoline

35 (115) 4-[(3-bromophenyl)amino]-7-{3-[2-(methoxycarbonyl)-pyrrolidin-1-yl]propyloxy}-6-methoxy-quinazoline

(116) 4-[(3-bromophenyl)amino]-7-{3-[3-(methoxycarbonyl)-4-methyl-piperazin-1-yl]propyloxy}-6-methoxy-quinazoline

40 (117) 4-[(3-bromophenyl)amino]-7-({1-[(ethoxycarbonyl)methyl]-piperidin-4-yl}methoxy)-6-ethoxy-quinazoline

45 (118) 4-[(3-bromophenyl)amino]-7-({1-[(ethoxycarbonyl)methyl]-piperidin-4-yl}methoxy)-6-(2-methoxyethoxy)-quinazoline

50 (119) 4-[(3-bromophenyl)amino]-7-(2-{1-[(ethoxycarbonyl)methyl]-piperidin-4-yl}ethoxy)-6-(2-methoxyethoxy)-quinazoline

5

(120) 4-[(3-bromophenyl)amino]-7-(2-{4-[(ethoxycarbonyl)methyl]-piperazin-1-yl}ethoxy)-6-(2-methoxyethoxy)-quinazoline

10

(121) 4-[(3-bromophenyl)amino]-7-(2-{4-[(ethoxycarbonyl)methyl]-piperazin-1-yl}ethoxy)-6-ethoxy-quinazoline

15

(122) 4-[(3-bromophenyl)amino]-7-(3-{1-[(ethoxycarbonyl)methyl]-piperidin-4-yl}propyloxy)-6-ethoxy-quinazoline

20

(123) 4-[(3-bromophenyl)amino]-7-(3-{4-[(ethoxycarbonyl)methyl]-piperazin-1-yl}propyloxy)-6-(2-methoxyethoxy)-quinazoline

(124) 4-[(3-bromophenyl)amino]-7-(3-{1-[(dimethoxyphosphoryl)methyl]-piperidin-4-yl}propyloxy)-6-methoxy-quinazoline

25

(125) 4-[(3-bromophenyl)amino]-7-(3-{4-[(dimethoxyphosphoryl)methyl]-piperazin-1-yl}propyloxy)-6-methoxy-quinazoline

30

(126) 4-[(3-bromophenyl)amino]-7-[3-(4-{[(methoxy)(ethyl)phosphoryl]methyl}-piperazin-1-yl)propyloxy]-6-methoxy-quinazoline

(127) 4-[(3-bromophenyl)amino]-7-[3-(1-{[(methoxy)(ethyl)phosphoryl]methyl}-piperidin-4-yl)propyloxy]-6-methoxy-quinazoline

35

(128) 4-[(3-bromophenyl)amino]-7-(3-{4-[1,2-bis(ethoxycarbonyl)ethyl]-piperazin-1-yl}propyloxy)-6-methoxy-quinazoline

40

(129) 4-[(3-bromophenyl)amino]-7-[3-(1-{1-[(ethoxycarbonyl)methyl]-2-(ethoxycarbonyl)-ethyl}-piperidin-4-yl)propyloxy]-6-methoxy-quinazoline

45

(130) 4-[(3-bromophenyl)amino]-7-(4-{1-[(ethoxycarbonyl)methyl]-piperidin-4-yl}butyloxy)-6-methoxy-quinazoline

50

(131) 4-[(3-bromophenyl)amino]-7-(4-{4-[(ethoxycarbonyl)methyl]-piperazin-1-yl}butyloxy)-6-methoxy-quinazoline

55

(132) 4-[(3-bromophenyl)amino]-7-(2-{N-[(ethoxycarbonyl)methyl]-N-methylamino}ethoxy)-6-methoxy-quinazoline

(133) 4-[(3-bromophenyl)amino]-7-(2-{N,N-bis[(ethoxycarbonyl)methyl]amino}ethoxy)-6-methoxy-quinazoline

(134) 4-[(3-bromophenyl)amino]-7-(2-{N-[(ethoxycarbonyl)methyl]-N-ethylamino}ethoxy)-6-methoxy-quinazoline

(135) 4-[(3-bromophenyl)amino]-7-(2-{N-[(ethoxycarbonyl)methyl]-N-(cyclopropylmethyl)-amino}ethoxy)-6-methoxy-quinazoline

(136) 4-[(3-bromophenyl)amino]-7-(2-{[(ethoxycarbonyl)methyl]-amino}ethoxy)-6-methoxy-quinazoline

(137) 4-[(3-bromophenyl)amino]-7-(2-{N-[(ethoxycarbonyl)methyl]-N-cyclopropyl-amino}ethoxy)-6-methoxy-quinazoline

(138) 4-[(3-bromophenyl)amino]-7-(2-{N-[(methoxycarbonyl)methyl]-N-methylamino}ethoxy)-6-methoxy-quinazoline

(139) 4-[(3-bromophenyl)amino]-7-(3-{N-[(methoxycarbonyl)methyl]-N-methylamino}propyloxy)-6-methoxy-quinazoline

(140) 4-[(3-bromophenyl)amino]-7-(3-{N,N-bis[(methoxycarbonyl)methyl]amino}propyloxy)-6-methoxy-quinazoline

(141) 4-[(3-bromophenyl)amino]-7-(3-{[(ethoxycarbonyl)methyl]-amino}propyloxy)-6-methoxy-quinazoline

(142) 4-[(3-bromophenyl)amino]-7-(4-{N-[(ethoxycarbonyl)methyl]-N-methylamino}butyloxy)-6-methoxy-quinazoline

(143) 4-[(3-bromophenyl)amino]-7-(4-{N,N-bis[(ethoxycarbonyl)methyl]amino}butyloxy)-6-methoxy-quinazoline

5

- 92 -

(144) 4-[(3-bromophenyl)amino]-7-({4-[(methoxycarbonyl)methyl]-2-oxo-morpholin-6-yl}methyloxy)-6-methoxy-quinazoline

10

(145) 4-[(3-bromophenyl)amino]-7-[(4-methyl-2-oxo-morpholin-6-yl)methyloxy]-6-methoxy-quinazoline

15

(146) 4-[(3-bromophenyl)amino]-7-[(2-oxo-morpholin-6-yl)methyloxy]-6-methoxy-quinazoline

20

(147) 4-[(4-amino-3,5-dibromo-phenyl)amino]-7-(3-{4-[(methoxycarbonyl)methyl]-piperazin-1-yl}propyloxy)-6-methoxy-quinazoline

25

(148) 4-[(4-amino-3,5-dibromo-phenyl)amino]-7-(3-{1-[(methoxycarbonyl)methyl]-piperidin-4-yl}propyloxy)-6-methoxy-quinazoline

30

(149) 4-[(3-bromophenyl)amino]-7-[3-(morpholino)propyloxy]-6-[(ethoxycarbonyl)methoxy]-quinazoline

35

(150) 4-[(3-bromophenyl)amino]-7-[2-(morpholino)ethoxy]-6-[(ethoxycarbonyl)methoxy]-quinazoline

40

(152) 4-[(3-bromophenyl)amino]-6-[3-(2-oxo-morpholin-4-yl)propyloxy]-7-methoxy-quinazoline

45

(153) 4-[(3-bromophenyl)amino]-6-[2-(3-methyl-2-oxo-morpholin-4-yl)ethoxy]-7-methoxy-quinazoline

50

(154) 4-[(3-bromophenyl)amino]-6-[2-(5,5-dimethyl-2-oxo-morpholin-4-yl)ethoxy]-7-methoxy-quinazoline

55

(155) 4-[(3-bromophenyl)amino]-6-(2-{4-[(ethoxycarbonyl)methyl]-piperazin-1-yl}ethoxy)-7-cyclopropylmethoxy-quinazoline

5

- 93 -

10

(156) 4-[(3-bromophenyl)amino]-6-(2-{4-[(ethoxycarbonyl)methyl]-piperazin-1-yl}ethoxy)-7-cyclobutyloxy-quinazoline

15

(157) 4-[(3-bromophenyl)amino]-6-(2-{4-[(ethoxycarbonyl)methyl]-piperazin-1-yl}ethoxy)-7-cyclopentyloxy-quinazoline

20

(158) 4-[(3-bromophenyl)amino]-6-(2-{4-[(ethoxycarbonyl)methyl]-piperazin-1-yl}ethoxy)-7-cyclohexyloxy-quinazoline

25

(159) 4-[(3-bromophenyl)amino]-6-(2-{4-[(ethoxycarbonyl)methyl]-piperazin-1-yl}ethoxy)-7-cyclopentylmethoxy-quinazoline

30

(160) 4-[(3-bromophenyl)amino]-6-(2-{4-[(ethoxycarbonyl)methyl]-piperazin-1-yl}ethoxy)-7-cyclohexylmethoxy-quinazoline

35

(161) 4-[(3-bromophenyl)amino]-6-(2-{4-[(benzyloxycarbonyl)methyl]-piperazin-1-yl}ethoxy)-7-methoxy-quinazoline

40

(162) 4-[(3-bromophenyl)amino]-6-(2-{4-[(phenyloxycarbonyl)methyl]-piperazin-1-yl}ethoxy)-7-methoxy-quinazoline

45

(163) 4-[(3-bromophenyl)amino]-6-(2-{4-[(indan-5-yloxy-carbonyl)methyl]-piperazin-1-yl}ethoxy)-7-methoxy-quinazoline

50

(164) 4-[(3-bromophenyl)amino]-6-(2-{4-[(cyclohexyloxy-carbonyl)methyl]-piperazin-1-yl}ethoxy)-7-methoxy-quinazoline

55

(165) 4-[(3-bromophenyl)amino]-6-(2-{4-[(cyclohexylmethoxy-carbonyl)methyl]-piperazin-1-yl}ethoxy)-7-methoxy-quinazoline

(166) 4-[(3-bromophenyl)amino]-6-cyclopropylmethoxy-7-(2-{4-[(ethoxycarbonyl)methyl]-piperazin-1-yl}ethoxy)quinazoline

(167) 4-[(3-bromophenyl)amino]-6-cyclobutyloxy-7-(2-{4-[(ethoxycarbonyl)methyl]-piperazin-1-yl}ethoxy)quinazoline

(168) 4-[(3-bromophenyl)amino]-6-cyclopentyloxy-7-(2-{4-[(ethoxycarbonyl)methyl]-piperazin-1-yl}ethoxy)quinazoline

(169) 4-[(3-bromophenyl)amino]-6-cyclopentylmethoxy-7-(2-{4-[(ethoxycarbonyl)methyl]-piperazin-1-yl}ethoxy)quinazoline

(170) 4-[(3-bromophenyl)amino]-6-cyclohexylmethoxy-7-(2-{4-[(ethoxycarbonyl)methyl]-piperazin-1-yl}ethoxy)quinazoline

(171) 4-[(3-bromophenyl)amino]-6-cyclohexyloxy-7-(2-{4-[(ethoxycarbonyl)methyl]-piperazin-1-yl}ethoxy)quinazoline

(172) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[2-(6,6-dimethyl-2-oxo-morpholin-4-yl)-ethoxy]-7-methoxy-quinazoline

(173) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[2-(6,6-dimethyl-2-oxo-morpholin-4-yl)-ethoxy]-7-cyclobutyloxy-quinazoline

(174) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[2-(6,6-dimethyl-2-oxo-morpholin-4-yl)-ethoxy]-7-cyclopentyloxy-quinazoline

(175) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[2-(6,6-dimethyl-2-oxo-morpholin-4-yl)-ethoxy]-7-cyclohexyloxy-quinazoline

(176) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[2-(6,6-dimethyl-2-oxo-morpholin-4-yl)-ethoxy]-7-cyclopropylmethoxy-quinazoline

(177) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[2-(6,6-dimethyl-2-oxo-morpholin-4-yl)-ethoxy]-7-cyclopentylmethoxy-quinazoline

(178) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[2-(6,6-dimethyl-2-oxo-morpholin-4-yl)-ethoxy]-7-cyclohexylmethoxy-quinazoline

(179) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{2-[N-(2-oxo-tetrahydrofuran-4-yl)-N-methyl-amino]-ethoxy}-7-methoxy-quinazoline

(180) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{2-[N-(2-oxo-tetrahydrofuran-4-yl)-N-methyl-amino]-ethoxy}-7-cyclopentyl-oxy-quinazoline

(181) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{2-[N-(2-oxo-tetrahydrofuran-4-yl)-N-methyl-amino]-ethoxy}-7-cyclopentyl-methoxy-quinazoline

(182) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{2-[N-(2-oxo-tetrahydrofuran-3-yl)-N-methyl-amino]-ethoxy}-7-methoxy-quinazoline

(183) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{2-[N-(2-oxo-tetrahydrofuran-3-yl)-N-methyl-amino]-ethoxy}-7-cyclopentyl-oxy-quinazoline

(184) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{2-[N-(2-oxo-tetrahydrofuran-3-yl)-N-methyl-amino]-ethoxy}-7-cyclopentyl-methoxy-quinazoline

(185) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[3-(6,6-dimethyl-2-oxo-morpholin-4-yl)-propyloxy]-7-methoxy-quinazoline

(186) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[3-(6,6-dimethyl-2-oxo-morpholin-4-yl)-propyloxy]-7-cyclopentyl-oxy-quinazoline

(187) 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[3-(6,6-dimethyl-2-oxo-morpholin-4-yl)-propyloxy]-7-cyclopentylmethoxy-quinazoline

(188) (R)-4-[(1-phenyl-ethyl)amino]-6-[3-(6,6-dimethyl-2-oxo-morpholin-4-yl)-propyloxy]-7-cyclopentyl-oxy-quinazoline

(189) 4-[(3-chloro-4-fluoro-phenyl)amino]-7-[2-(6,6-dimethyl-2-oxo-morpholin-4-yl)-ethoxy]-6-methoxy-quinazoline

(190) 4-[(3-chloro-4-fluoro-phenyl)amino]-7-[2-(6,6-dimethyl-2-oxo-morpholin-4-yl)-ethoxy]-6-cyclobutyloxy-quinazoline

(191) 4-[(3-chloro-4-fluoro-phenyl)amino]-7-[2-(6,6-dimethyl-2-oxo-morpholin-4-yl)-ethoxy]-6-cyclopentyloxy-quinazoline

(192) 4-[(3-chloro-4-fluoro-phenyl)amino]-7-[2-(6,6-dimethyl-2-oxo-morpholin-4-yl)-ethoxy]-6-cyclohexyloxy-quinazoline

(193) 4-[(3-chloro-4-fluoro-phenyl)amino]-7-[2-(6,6-dimethyl-2-oxo-morpholin-4-yl)-ethoxy]-6-cyclopropylmethoxy-quinazoline

(194) 4-[(3-chloro-4-fluoro-phenyl)amino]-7-[2-(6,6-dimethyl-2-oxo-morpholin-4-yl)-ethoxy]-6-cyclopentylmethoxy-quinazoline

(195) 4-[(3-chloro-4-fluoro-phenyl)amino]-7-[2-(6,6-dimethyl-2-oxo-morpholin-4-yl)-ethoxy]-6-cyclohexylmethoxy-quinazoline

(196) 4-[(3-chloro-4-fluoro-phenyl)amino]-7-{2-[N-(2-oxo-tetrahydrofuran-4-yl)-N-methyl-amino]-ethoxy}-6-methoxy-quinazoline

(197) 4-[(3-chloro-4-fluoro-phenyl)amino]-7-{2-[N-(2-oxo-tetrahydrofuran-4-yl)-N-methyl-amino]-ethoxy}-6-cyclopentyl-oxy-quinazoline

(198) 4-[(3-chloro-4-fluoro-phenyl)amino]-7-{2-[N-(2-oxo-tetrahydrofuran-4-yl)-N-methyl-amino]-ethoxy}-6-cyclopentyl-methoxy-quinazoline

(199) 4-[(3-chloro-4-fluoro-phenyl)amino]-7-{2-[N-(2-oxo-tetrahydrofuran-3-yl)-N-methyl-amino]-ethoxy}-6-methoxy-quinazoline

(200) 4-[(3-chloro-4-fluoro-phenyl)amino]-7-{2-[N-(2-oxo-tetrahydrofuran-3-yl)-N-methyl-amino]-ethoxy}-6-cyclopentyl-oxy-quinazoline

(201) 4-[(3-chloro-4-fluoro-phenyl)amino]-7-{2-[N-(2-oxo-tetrahydrofuran-3-yl)-N-methyl-amino]-ethoxy}-6-cyclopentyl-methoxy-quinazoline

(202) 4-[(3-chloro-4-fluoro-phenyl)amino]-7-[3-(6,6-dimethyl-2-oxo-morpholin-4-yl)-propyloxy]-6-methoxy-quinazoline

(203) 4-[(3-chloro-4-fluoro-phenyl)amino]-7-[3-(6,6-dimethyl-2-oxo-morpholin-4-yl)-propyloxy]-6-cyclopentyloxy-quinazoline

(204) 4-[(3-chloro-4-fluoro-phenyl)amino]-7-[3-(6,6-dimethyl-2-oxo-morpholin-4-yl)-propyloxy]-6-cyclopentylmethoxy-quinazoline

(205) (R)-4-[(1-phenyl-ethyl)amino]-7-[3-(6,6-dimethyl-2-oxo-morpholin-4-yl)-propyloxy]-6-cyclopentyloxy-quinazoline

Example 6

Coated tablets containing 75 mg of active substance

1 tablet core contains:

active substance	75.0 mg
calcium phosphate	93.0 mg
corn starch	35.5 mg
polyvinylpyrrolidone	10.0 mg
hydroxypropylmethylcellulose	15.0 mg
magnesium stearate	<u>1.5 mg</u>
	230.0 mg

Preparation:

The active substance is mixed with calcium phosphate, corn starch, polyvinylpyrrolidone, hydroxypropylmethylcellulose and half the specified amount of magnesium stearate. Blanks 13 mm in diameter are produced in a tablet-making machine and these are then rubbed through a screen with a mesh size of 1.5 mm

5 using a suitable machine and mixed with the rest of the
magnesium stearate. This granulate is compressed in a tablet-
10 making machine to form tablets of the desired shape.

Weight of core: 230 mg

die: 9 mm, convex

The tablet cores thus produced are coated with a film
15 consisting essentially of hydroxypropylmethylcellulose. The
finished film-coated tablets are polished with beeswax.

Weight of coated tablet: 245 mg.

20 Example 7

Tablets containing 100 mg of active substance

Composition:

25 1 tablet contains:

active substance	100.0 mg
lactose	80.0 mg
corn starch	34.0 mg
30 polyvinylpyrrolidone	4.0 mg
magnesium stearate	<u>2.0 mg</u>
	220.0 mg

35 Method of Preparation:

The active substance, lactose and starch are mixed together and
uniformly moistened with an aqueous solution of the polyvinyl-
pyrrolidone. After the moist composition has been screened
40 (2.0 mm mesh size) and dried in a rack-type drier at 50°C it is
screened again (1.5 mm mesh size) and the lubricant is added.
The finished mixture is compressed to form tablets.

Weight of tablet: 220 mg

45 Diameter: 10 mm, biplanar, facettted on both sides
and notched on one side.

5

- 99 -

Example 8

10

Tablets containing 150 mg of active substance

Composition:

1 tablet contains:

15

active substance	150.0 mg
powdered lactose	89.0 mg
corn starch	40.0 mg
colloidal silica	10.0 mg
polyvinylpyrrolidone	10.0 mg
magnesium stearate	<u>1.0 mg</u>

300.0 mg

20

Preparation:

25

The active substance mixed with lactose, corn starch and silica is moistened with a 20% aqueous polyvinylpyrrolidone solution and passed through a screen with a mesh size of 1.5 mm. The granules, dried at 45°C, are passed through the same screen again and mixed with the specified amount of magnesium stearate. Tablets are pressed from the mixture.

30

Weight of tablet: 300 mg

die: 10 mm, flat

35

Example 9

40

Hard gelatine capsules containing 150 mg of active substance

1 capsule contains:

45

active substance		150.0 mg
corn starch (dried)	approx.	180.0 mg
lactose (powdered)	approx.	87.0 mg
magnesium stearate		<u>3.0 mg</u>
	approx.	420.0 mg

50

55

5

- 100 -

Preparation:

10

The active substance is mixed with the excipients, passed through a screen with a mesh size of 0.75 mm and homogeneously mixed using a suitable apparatus. The finished mixture is packed into size 1 hard gelatine capsules.

15

Capsule filling: approx. 320 mg

Capsule shell: size 1 hard gelatine capsule.

Example 10

20

Suppositories containing 150 mg of active substance

25

1 suppository contains:

active substance	150.0 mg
polyethyleneglycol 1500	550.0 mg
polyethyleneglycol 6000	460.0 mg
polyoxyethylene sorbitan monostearate	<u>840.0 mg</u>
	2,000.0 mg

30

Preparation:

35

After the suppository mass has been melted the active substance is homogeneously distributed therein and the melt is poured into chilled moulds.

Example 11

40

Suspension containing 50 mg of active substance

45

100 ml of suspension contain:

active substance	1.00 g
carboxymethylcellulose-Na-salt	0.10 g
methyl p-hydroxybenzoate	0.05 g
propyl p-hydroxybenzoate	0.01 g
glucose	10.00 g
glycerol	5.00 g
70% sorbitol solution	20.00 g

50

55

5

- 101 -

flavouring		0.30 g
dist. water	ad	100 ml

10

Preparation:

The distilled water is heated to 70°C. The methyl and propyl p-hydroxybenzoates together with the glycerol and sodium salt of carboxymethylcellulose are dissolved therein with stirring. The solution is cooled to ambient temperature and the active substance is added and homogeneously dispersed therein with stirring. After the sugar, the sorbitol solution and the flavouring have been added and dissolved, the suspension is evacuated with stirring to eliminate air.

15

20

5 ml of suspension contain 50 mg of active substance.

25

Example 12Ampoules containing 10 mg active substance

30

Composition:

active substance		10.0 mg
0.01 N hydrochloric acid q.s.		
double-distilled water	ad	2.0 ml

35

Preparation:

The active substance is dissolved in the necessary amount of 0.01 N HCl, made isotonic with common salt, filtered sterile and transferred into 2 ml ampoules.

40

Example 13Ampoules containing 50 mg of active substance

45

Composition:

active substance		50.0 mg
0.01 N hydrochloric acid q.s.		
double-distilled water	ad	10.0 ml

50

55

5

- 102 -

Preparation:

10

The active substance is dissolved in the necessary amount of 0.01 N HCl, made isotonic with common salt, filtered sterile and transferred into 10 ml ampoules.

15

Example 14

Capsules for powder inhalation containing 5 mg of active substance

20

1 capsule contains:

25

active substance	5.0 mg
lactose for inhalation	<u>15.0 mg</u>
	20.0 mg

30

Preparation:

The active substance is mixed with lactose for inhalation. The mixture is packed into capsules in a capsule-making machine (weight of the empty capsule approx. 50 mg).

35

weight of capsule: 70.0 mg
size of capsule = 3

Example 15

40

Solution for inhalation for hand-held nebulisers containing 2.5 mg active substance

1 spray contains:

45

50

active substance	2.500 mg
benzalkonium chloride	0.001 mg
1N hydrochloric acid q.s.	
ethanol/water (50/50)	ad 15.000 mg

55

5

Preparation:

10

The active substance and benzalkonium chloride are dissolved in ethanol/water (50/50). The pH of the solution is adjusted with 1N hydrochloric acid. The resulting solution is filtered and transferred into suitable containers for use in hand-held nebulisers (cartridges).

15

Contents of the container: 4.5 g

20

25

30

35

40

45

50

55

Claims

5

10

15

20

25

30

35

40

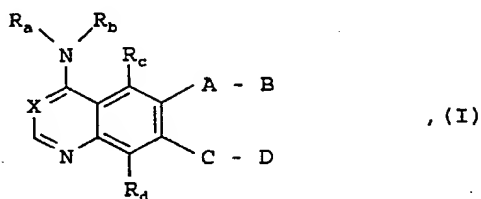
45

50

55

Patent Claims

1. Bicyclic heterocycles of general formula



wherein

R_a denotes a hydrogen atom or a C_{1-4} -alkyl group,

R_b denotes a phenyl, benzyl or 1-phenylethyl group wherein the phenyl nucleus is substituted in each case by the groups R_1 to R_3 , whilst

R_1 and R_2 , which may be identical or different, each denote a hydrogen, fluorine, chlorine, bromine or iodine atom,

a C_{1-4} -alkyl, hydroxy, C_{1-4} -alkoxy, C_{3-6} -cycloalkyl, C_{4-6} -cycloalkoxy, C_{2-5} -alkenyl or C_{2-5} -alkynyl group,

an aryl, aryloxy, arylmethyl or arylmethoxy group,

a C_{3-5} -alkenyloxy or C_{3-5} -alkynyloxy group, whilst the unsaturated moiety may not be linked to the oxygen atom,

a C_{1-4} -alkylsulphenyl, C_{1-4} -alkylsulphinyl, C_{1-4} -alkylsulphonyl, C_{1-4} -alkylsulphonyloxy, trifluoromethylsulphenyl, trifluoromethylsulphinyl or trifluoromethylsulphonyl group,

a methyl or methoxy group substituted by 1 to 3 fluorine atoms,

an ethyl or ethoxy group substituted by 1 to 5 fluorine atoms,

a cyano or nitro group or an amino group optionally substituted by one or two C₁₋₄-alkyl groups, whilst the substituents may be identical or different,

or R₁ together with R₂, if they are bound to adjacent carbon atoms, denote a -CH=CH-CH=CH, -CH=CH-NH or -CH=N-NH group and

R₃ denotes a hydrogen, fluorine, chlorine or bromine atom,

a C₁₋₄-alkyl, trifluoromethyl or C₁₋₄-alkoxy group,

R_c and R_d, which may be identical or different, each denote a hydrogen, fluorine or chlorine atom, a methoxy group or a methyl group optionally substituted by a methoxy, dimethylamino, diethylamino, pyrrolidino, piperidino or morpholino group,

X denotes a methine group substituted by a cyano group or a nitrogen atom,

A denotes an -O-C₁₋₆-alkylene, -O-C₄₋₇-cycloalkylene, -O-C₁₋₃-alkylene-C₃₋₇-cycloalkylene, -O-C₄₋₇-cycloalkylene-C₁₋₃-alkylene or -O-C₁₋₃-alkylene-C₃₋₇-cycloalkylene-C₁₋₃-alkylene group, whilst the oxygen atom of the abovementioned groups in each case is linked to the bicyclic heteroaromatic ring,

an -O-C₁₋₆-alkylene group which is substituted by an R_eO-CO or R_eO-CO-C₁₋₄-alkyl group, whilst R_e is as hereinafter defined and the oxygen atom of the abovementioned -O-C₁₋₆-alkylene groups in each case is linked to the bicyclic heteroaromatic ring,

an -O-C₂₋₆-alkylene group which is substituted from position 2 onwards by a hydroxy, C₁₋₄-alkoxy, amino, C₁₋₄-alkylamino, di-

(C₁₋₄-alkyl)-amino, pyrrolidino, piperidino, morpholino, piperazino or 4-(C₁₋₄-alkyl)-piperazino group and the oxygen atom of the abovementioned-O-C₁₋₆-alkylene groups in each case is linked to the bicyclic heteroaromatic ring,

a -C₁₋₆-alkylene group,

an -NR₄-C₁₋₆-alkylene, -NR₄-C₃₋₇-cycloalkylene, -NR₄-C₁₋₃-alkylene-C₃₋₇-cycloalkylene, -NR₄-C₃₋₇-cycloalkylene-C₁₋₃-alkylene or -NR₄-C₁₋₃-alkylene-C₃₋₇-cycloalkylene-C₁₋₃-alkylene group, whilst the -NR₄- moiety of the abovementioned groups in each case is linked to the bicyclic heteroaromatic ring, and

R₄ denotes a hydrogen atom or a C₁₋₄-alkyl group,

an oxygen atom, this being linked to a carbon atom of the group B, or

a NR₄ group, the latter being linked to a carbon atom of the group B and R₄ being as hereinbefore defined,

B denotes an R₆O-CO-alkylene-NR₅, (R₆O-PO-OR₆)-alkylene-NR₅ or (R₆O-PO-R₆)-alkylene-NR₅ group wherein in each case the alkylene moiety, which is straight-chained and contains 1 to 6 carbon atoms, may additionally be substituted by one or two C₁₋₂-alkyl groups or by an R₆O-CO or R₆O-CO-C₁₋₂-alkyl group, whilst

R₅ denotes a hydrogen atom,

a C₁₋₄-alkyl group which may be substituted by an R₆O-CO, (R₆O-PO-OR₆) or (R₆O-PO-R₆) group,

a C₂₋₄-alkyl group which is substituted from position 2 by a hydroxy, C₁₋₄-alkoxy, amino, C₁₋₄-alkylamino or di-(C₁₋₄-alkyl)-amino group or by a 4- to 7-membered alkyleneimino group, whilst in the abovementioned 6- to 7-membered alkyleneimino groups in each case a methylene group in the

4 position may be replaced by an oxygen or sulphur atom, by
a sulphinyl, sulphonyl, imino or N-(C₁₋₄-alkyl)-imino group,

a C₁₋₇-cycloalkyl or C₃₋₇-cycloalkyl-C₁₋₃-alkyl group,

R₆, R₇ and R₈, which may be identical or different, in each
case denote a hydrogen atom,

a C₁₋₈-alkyl group which may be substituted from position 2
onwards by a hydroxy, C₁₋₄-alkoxy, amino, C₁₋₄-alkylamino or
di-(C₁₋₄-alkyl)-amino group or by a 4- to 7-membered alky-
leneimino group, whilst in the abovementioned 6- to 7-mem-
bered alkyleneimino groups in each case a methylene group
in the 4 position may be replaced by an oxygen or sulphur
atom, by a sulphinyl, sulphonyl, imino or N-(C₁₋₄-alkyl)-
imino group,

a C₄₋₇-cycloalkyl group optionally substituted by 1 or 2
methyl groups,

a C₃₋₅-alkenyl or C₃₋₅-alkynyl group, whilst the unsaturated
moiety may not be linked to the oxygen atom,

a C₃₋₇-cycloalkyl-C₁₋₄-alkyl, aryl, aryl-C₁₋₄-alkyl or R₉CO-O-
(R₈CR₄) group, whilst

R₆ and R₇, which may be identical or different, in each
case denote a hydrogen atom or a C₁₋₄-alkyl group and

R₉ denotes a C₁₋₄-alkyl, C₃₋₇-cycloalkyl, C₁₋₄-alkoxy or
C₃₋₇-cycloalkoxy group,

and R₈ denotes a C₁₋₄-alkyl, aryl or aryl-C₁₋₄-alkyl group,

a 4- to 7-membered alkyleneimino group which is substituted by
an R₆O-CO, (R₇O-PO-OR₈), (R₇O-PO-R₈), R₆O-CO-C₁₋₄-alkyl, bis-

(R₆O-CO)-C₁₋₄-alkyl, (R₇O-PO-OR₈)-C₁₋₄-alkyl or (R₇O-PO-R₉)-C₁₋₄-alkyl group wherein R₆ to R₉ are as hereinbefore defined,

a 4- to 7-membered alkyleneimino group which is substituted by two R₆O-CO or R₆O-CO-C₁₋₄-alkyl groups or by an R₆OCO group and an R₆O-CO-C₁₋₄-alkyl group wherein R₆ is as hereinbefore defined,

a piperazino or homopiperazino group which is substituted in the 4 position by the group R₁₀ and additionally at a cyclic carbon atom by an R₆O-CO, (R₇O-PO-OR₈), (R₇O-PO-R₉), R₆O-CO-C₁₋₄-alkyl, bis-(R₆O-CO)-C₁₋₄-alkyl, (R₇O-PO-OR₈)-C₁₋₄-alkyl or (R₇O-PO-R₉)-C₁₋₄-alkyl group wherein R₆ to R₉ are as hereinbefore defined and

R₁₀ denotes a hydrogen atom, a C₁₋₄-alkyl, formyl, C₁₋₄-alkylcarbonyl or C₁₋₄-alkylsulphonyl group,

a piperazino or homopiperazino group which is substituted in the 4 position by the group R₁₀ and is additionally substituted at cyclic carbon atoms by two R₆O-CO or R₆O-CO-C₁₋₄-alkyl groups or by an R₆O-CO group and an R₆O-CO-C₁₋₄-alkyl group wherein R₆ and R₁₀ are as hereinbefore defined,

a piperazino or homopiperazino group which is substituted in each case in the 4 position by an R₆O-CO-C₁₋₄-alkyl, bis-(R₆O-CO)-C₁₋₄-alkyl, (R₇O-PO-OR₈)-C₁₋₄-alkyl or (R₇O-PO-R₉)-C₁₋₄-alkyl group wherein R₆ to R₉ are as hereinbefore defined,

a piperazino or homopiperazino group which is substituted in the 4 position by an R₆O-CO-C₁₋₄-alkyl, bis-(R₆O-CO)-C₁₋₄-alkyl, (R₇O-PO-OR₈)-C₁₋₄-alkyl or (R₇O-PO-R₉)-C₁₋₄-alkyl group and is additionally substituted at cyclic carbon atoms by one or two R₆O-CO or R₆O-CO-C₁₋₄-alkyl groups or by an R₆O-CO group and an R₆O-CO-C₁₋₄-alkyl group wherein R₆ to R₉ are as hereinbefore defined,

5

- 109 -

a morpholino or homomorpholino group which is substituted in each case by an R_6O-CO , $(R_7O-PO-OR_8)$, $(R_7O-PO-R_9)$, $R_6O-CO-C_{1-4}$ -alkyl, bis- $(R_6O-CO)-C_{1-4}$ -alkyl, $(R_7O-PO-OR_8)-C_{1-4}$ -alkyl or $(R_7O-PO-R_9)-C_{1-4}$ -alkyl group wherein R_6 to R_9 are as hereinbefore defined,

10

15

a morpholino or homomorpholino group which is substituted by two R_6O-CO or $R_6O-CO-C_{1-4}$ -alkyl groups or by an R_6O-CO group and an $R_6O-CO-C_{1-4}$ -alkyl group wherein R_6 is as hereinbefore defined,

20

a pyrrolidinyl, piperidinyl or hexahydroazepinyl group substituted in the 1 position by the group R_{10} , whilst the abovementioned 5 to 7-membered rings are in each case additionally substituted at a carbon atom by an R_6O-CO , $(R_7O-PO-OR_8)$, $(R_7O-PO-R_9)$, $R_6O-CO-C_{1-4}$ -alkyl, bis- $(R_6O-CO)-C_{1-4}$ -alkyl, $(R_7O-PO-OR_8)-C_{1-4}$ -alkyl or $(R_7O-PO-R_9)-C_{1-4}$ -alkyl group wherein R_6 to R_{10} are as hereinbefore defined,

25

30

a pyrrolidinyl, piperidinyl or hexahydroazepinyl group substituted in the 1 position by the group R_{10} , whilst the abovementioned 5 to 7-membered rings in each case are additionally substituted at carbon atoms by two R_6O-CO or $R_6O-CO-C_{1-4}$ -alkyl groups or by an R_6O-CO group and an $R_6O-CO-C_{1-4}$ -alkyl group wherein R_6 and R_{10} are as hereinbefore defined,

35

a pyrrolidinyl, piperidinyl or hexahydroazepinyl group substituted in the 1 position by an $R_6O-CO-C_{1-4}$ -alkyl, bis- $(R_6O-CO)-C_{1-4}$ -alkyl, $(R_7O-PO-OR_8)-C_{1-4}$ -alkyl or $(R_7O-PO-R_9)-C_{1-4}$ -alkyl group wherein R_6 to R_9 are as hereinbefore defined,

40

a pyrrolidinyl, piperidinyl or hexahydroazepinyl group substituted in the 1 position by an $R_6O-CO-C_{1-4}$ -alkyl, bis- $(R_6O-CO)-C_{1-4}$ -alkyl, $(R_7O-PO-OR_8)-C_{1-4}$ -alkyl or $(R_7O-PO-R_9)-C_{1-4}$ -alkyl group, whilst the abovementioned 5- to 7-membered rings in each case are additionally substituted at carbon atoms by one or two R_6O-CO or $R_6O-CO-C_{1-4}$ -alkyl groups or by an R_6O-CO group and an

45

50

55

5

- 110 -

$R_6O-CO-C_{1-4}$ -alkyl group wherein R_6 to R_9 are as hereinbefore defined,

10

a 2-oxo-morpholino group which may be substituted by 1 to 4 C_{1-2} -alkyl groups,

15

a 2-oxo-morpholinyl group which is substituted in the 4 position by a hydrogen atom, by a C_{1-4} -alkyl, $R_6O-CO-C_{1-4}$ -alkyl, $(R_7O-PO-OR_8)-C_{1-4}$ -alkyl or $(R_7O-PO-R_9)-C_{1-4}$ -alkyl group, whilst R_6 to R_9 are as hereinbefore defined and the abovementioned 2-oxo-morpholinyl groups in each case are linked to a carbon atom of the group A,

20

an $R_{11}NR_5$ group wherein R_5 is as hereinbefore defined and

25

R_{11} denotes a 2-oxo-tetrahydrofuran-3-yl, 2-oxo-tetrahydrofuran-4-yl, 2-oxo-tetrahydropyran-3-yl, 2-oxo-tetrahydropyran-4-yl or 2-oxo-tetrahydropyran-5-yl group optionally substituted by one or two methyl groups,

30

or A and B together denotes a hydrogen, fluorine or chlorine atom,

35

a C_{1-6} -alkoxy group,

a C_{2-6} -alkoxy group which is substituted from position 2 onwards by a hydroxy, C_{1-4} -alkoxy, amino, C_{1-4} -alkylamino, di- $(C_{1-4}$ -alkyl)-amino, pyrrolidino, piperidino, hexahydroazepino, morpholino, homomorpholino, piperazino, 4- $(C_{1-4}$ -alkyl)-piperazino, homopiperazino, 4- $(C_{1-4}$ -alkyl)-homopiperazino or 1-imidazolyl group,

45

a C_{1-4} -alkoxy group which is substituted by a pyrrolidinyl, piperidinyl or hexahydroazepinyl group substituted in the 1 position by the group R_{10} , whilst R_{10} is as hereinbefore defined,

50

55

5 a C₁₋₆-alkoxy group which is substituted by an R₆O-CO, (R₆O-PO-OR₆) or (R₆O-PO-R₆) group, whilst R₆ to R₈ are as hereinbefore defined,

10 a C₃₋₇-cycloalkoxy or C₃₋₇-cycloalkyl-C₁₋₄-alkoxy group,

15 an amino, C₁₋₄-alkylamino, di-(C₁₋₄-alkyl)-amino, pyrrolidino, piperidino, hexahydroazepino, morpholino, homomorpholino, piperazino, 4-(C₁₋₄-alkyl)-piperazino, homopiperazino or 4-(C₁₋₄-alkyl)-homopiperazino group,

20 a 2-oxo-morpholino group which may be substituted by 1 or 2 methyl groups,

25 C denotes an -O-C₁₋₆-alkylene, -O-C₃₋₇-cycloalkylene, -O-C₁₋₃-alkylene-C₃₋₇-cycloalkylene, -O-C₃₋₇-cycloalkylene-C₁₋₃-alkylene or -O-C₁₋₃-alkylene-C₃₋₇-cycloalkylene-C₁₋₃-alkylene group, whilst the oxygen atom of the abovementioned group in each case is linked to the bicyclic heteroaromatic ring,

30 an -O-C₁₋₆-alkylene group which is substituted by an R₆O-CO or R₆O-CO-C₁₋₄-alkyl group, whilst R₆ is as hereinbefore defined and the oxygen atom of the abovementioned-O-C₁₋₆-alkylene groups in each case is linked to the bicyclic heteroaromatic ring,

35 an -O-C₁₋₆-alkylene group which is substituted from position 2 by a hydroxy, C₁₋₄-alkoxy, amino, C₁₋₄-alkylamino, di-(C₁₋₄-alkyl)-amino, pyrrolidino, piperidino, morpholino, piperazino or 4-(C₁₋₄-alkyl)-piperazino group and the oxygen atom of the abovementioned-O-C₁₋₆-alkylene groups in each case is linked to the bicyclic heteroaromatic ring,

40 a -C₁₋₆-alkylene group,

45 an -NR₄-C₁₋₆-alkylene, -NR₄-C₃₋₇-cycloalkylene, -NR₄-C₁₋₃-alkylene-C₃₋₇-cycloalkylene, -NR₄-C₃₋₇-cycloalkylene-C₁₋₃-alkylene or -NR₄-C₁₋₃-alkylene-C₃₋₇-cycloalkylene-C₁₋₃-alkylene group, whilst

the -NR₄- moiety of the abovementioned groups in each case is linked to the bicyclic heteroaromatic ring and R₄ is as hereinbefore defined,

an oxygen atom, which is linked to a carbon atom of the group D, or

a NR₄ group, where the latter is linked to a carbon atom of the group D and R₄ is as hereinbefore defined,

D denotes an R₆O-CO-alkylene-NR₅, (R₇O-PO-OR₈)-alkylene-NR₅ or (R₇O-PO-R₉)-alkylene-NR₅ group wherein in each case the alkylene moiety, which is straight-chained and contains 1 to 6 carbon atoms, may additionally be substituted by one or two C₁₋₂-alkyl groups or by an R₆O-CO or R₆O-CO-C₁₋₂-alkyl group, whilst R₅ to R₉ are as hereinbefore defined,

a 4- to 7-membered alkyleneimino group which is substituted by an R₆O-CO, (R₇O-PO-OR₈), (R₇O-PO-R₉), R₆O-CO-C₁₋₄-alkyl, bis-(R₆O-CO)-C₁₋₄-alkyl, (R₇O-PO-OR₈)-C₁₋₄-alkyl or (R₇O-PO-R₉)-C₁₋₄-alkyl group wherein R₆ to R₉ are as hereinbefore defined,

a 4- to 7-membered alkyleneimino group which is substituted by two R₆O-CO or R₆O-CO-C₁₋₄-alkyl groups or by an R₆OCO group and an R₆O-CO-C₁₋₄-alkyl group wherein R₆ is as hereinbefore defined,

a piperazino or homopiperazino group which is substituted in the 4 position by the group R₁₀ and additionally at a cyclic carbon atom by an R₆O-CO, (R₇O-PO-OR₈), (R₇O-PO-R₉), R₆O-CO-C₁₋₄-alkyl, bis-(R₆O-CO)-C₁₋₄-alkyl, (R₇O-PO-OR₈)-C₁₋₄-alkyl or (R₇O-PO-R₉)-C₁₋₄-alkyl group wherein R₆ to R₁₀ are as hereinbefore defined,

a piperazino or homopiperazino group which is substituted in the 4 position by the group R₁₀ and is additionally substituted at cyclic carbon atoms by two R₆O-CO or R₆O-CO-C₁₋₄-alkyl groups

or by an R_6 -O-CO group and an R_6 -O-CO- C_{1-4} -alkyl group wherein R_6 and R_{10} are as hereinbefore defined,

a piperazino or homopiperazino group which is substituted in each case in the 4 position by an R_6 -O-CO- C_{1-4} -alkyl, bis- $(R_6$ -O-CO)- C_{1-4} -alkyl, $(R_7$ -O-PO-OR₈)- C_{1-4} -alkyl or $(R_7$ -O-PO- R_9)- C_{1-4} -alkyl group wherein R_6 to R_9 are as hereinbefore defined,

a piperazino or homopiperazino group which is substituted in the 4 position by an R_6 -O-CO- C_{1-4} -alkyl, bis- $(R_6$ -O-CO)- C_{1-4} -alkyl, $(R_7$ -O-PO-OR₈)- C_{1-4} -alkyl or $(R_7$ -O-PO- R_9)- C_{1-4} -alkyl group and is additionally substituted at cyclic carbon atoms by one or two R_6 -O-CO or R_6 -O-CO- C_{1-4} -alkyl groups or by an R_6 -O-CO group and an R_6 -O-CO- C_{1-4} -alkyl group wherein R_6 to R_9 are as hereinbefore defined,

a morpholino or homomorpholino group which is substituted in each case by an R_6 -O-CO, $(R_7$ -O-PO-OR₈), $(R_7$ -O-PO- R_9), R_6 -O-CO- C_{1-4} -alkyl, bis- $(R_6$ -O-CO)- C_{1-4} -alkyl, $(R_7$ -O-PO-OR₈)- C_{1-4} -alkyl or $(R_7$ -O-PO- R_9)- C_{1-4} -alkyl group wherein R_6 to R_9 are as hereinbefore defined,

a morpholino or homomorpholino group which is substituted by two R_6 -O-CO or R_6 -O-CO- C_{1-4} -alkyl groups or by an R_6 -O-CO group and an R_6 -O-CO- C_{1-4} -alkyl group wherein R_6 is as hereinbefore defined,

a pyrrolidinyl, piperidinyl or hexahydroazepinyl group substituted in the 1 position by the group R_{10} , whilst the abovementioned 5- to 7-membered rings in each case are additionally substituted at a carbon atom by an R_6 -O-CO, $(R_7$ -O-PO-OR₈), $(R_7$ -O-PO- R_9), R_6 -O-CO- C_{1-4} -alkyl, bis- $(R_6$ -O-CO)- C_{1-4} -alkyl, $(R_7$ -O-PO-OR₈)- C_{1-4} -alkyl or $(R_7$ -O-PO- R_9)- C_{1-4} -alkyl group wherein R_6 to R_{10} are as hereinbefore defined,

a pyrrolidinyl, piperidinyl or hexahydroazepinyl group substituted in the 1 position by the group R_{10} , whilst the abovementioned 5- to 7-membered rings are in each case additionally

5

- 114 -

10

substituted at carbon atoms by two R_6O-CO or $R_6O-CO-C_{1-4}$ -alkyl groups or by an R_6O-CO group and an $R_6O-CO-C_{1-4}$ -alkyl group wherein R_6 and R_{10} are as hereinbefore defined,

15

a pyrrolidinyl, piperidinyl or hexahydroazepinyl group substituted in the 1 position by an $R_6O-CO-C_{1-4}$ -alkyl, bis- $(R_6O-CO)-C_{1-4}$ -alkyl, $(R_7O-PO-OR_8)-C_{1-4}$ -alkyl or $(R_7O-PO-R_9)-C_{1-4}$ -alkyl group wherein R_6 to R_9 are as hereinbefore defined,

20

a pyrrolidinyl, piperidinyl or hexahydroazepinyl group substituted in the 1 position by an $R_6O-CO-C_{1-4}$ -alkyl, bis- $(R_6O-CO)-C_{1-4}$ -alkyl, $(R_7O-PO-OR_8)-C_{1-4}$ -alkyl or $(R_7O-PO-R_9)-C_{1-4}$ -alkyl group, whilst the abovementioned 5- to 7-membered rings are in each case additionally substituted at carbon atoms by one or two

25

R_6O-CO or $R_6O-CO-C_{1-4}$ -alkyl groups or by an R_6O-CO group and an $R_6O-CO-C_{1-4}$ -alkyl group wherein R_6 to R_9 are as hereinbefore defined,

30

a 2-oxo-morpholino group which may be substituted by 1 to 4 C_{1-4} -alkyl groups,

35

a 2-oxo-morpholinyl group which is substituted in the 4 position by a hydrogen atom, by a C_{1-4} -alkyl, $R_6O-CO-C_{1-4}$ -alkyl, $(R_7O-PO-OR_8)-C_{1-4}$ -alkyl or $(R_7O-PO-R_9)-C_{1-4}$ -alkyl group, whilst R_6 to R_9 are as hereinbefore defined and the abovementioned 2-oxo-morpholinyl groups are in each case linked to a carbon atom of the group C,

40

an $R_{11}NR_5$ group wherein R_5 and R_{11} are as hereinbefore defined, or

45

C and D together denote a hydrogen, fluorine or chlorine atom,

a C_{1-6} -alkoxy group,

50

a C_{2-6} -alkoxy group which is substituted from position 2 by a hydroxy, C_{1-4} -alkoxy, amino, C_{1-4} -alkylamino, di- $(C_{1-4}$ -alkyl)-

55

5

- 115 -

10

amino, pyrrolidino, piperidino, hexahydroazepino, morpholino, homomorpholino, piperazino, 4-(C₁₋₄-alkyl)-piperazino, homopiperazino, 4-(C₁₋₄-alkyl)-homopiperazino or 1-imidazolyl group,

15

a C₁₋₄-alkoxy group which is substituted by a pyrrolidinyl, piperidinyl or hexahydroazepinyl group substituted in the 1 position by the group R₁₀, whilst R₁₀ is as hereinbefore defined,

20

a C₁₋₆-alkoxy group which is substituted by an R₆O-CO, (R₆O-PO-OR₆) or (R₆O-PO-R₆) group, whilst R₆ to R₉ are as hereinbefore defined,

25

a C₃₋₇-cycloalkoxy or C₃₋₇-cycloalkyl-C₁₋₄-alkoxy group

30

an amino, C₁₋₄-alkylamino, di-(C₁₋₄-alkyl)-amino, pyrrolidino, piperidino, hexahydroazepino, morpholino, homomorpholino, piperazino, 4-(C₁₋₄-alkyl)-piperazino, homopiperazino or 4-(C₁₋₄-alkyl)-homopiperazino group,

35

a 2-oxo-morpholino group which may be substituted by 1 or 2 methyl groups,

40

with the proviso that at least one of the groups B or D or A together with B or C together with D contains an optionally substituted 2-oxo-morpholinyl group, an (R₆O-PO-OR₆) or (R₆O-PO-R₆) group, or

45

that at least one of the groups B or D contains an optionally substituted 2-oxo-tetrahydrofuran-3-yl, 2-oxo-tetrahydrofuran-4-yl, 2-oxo-tetrahydropyran-3-yl, 2-oxo-tetrahydropyran-4-yl or 2-oxo-tetrahydropyran-5-yl group, or

50

that at least one of the groups A, B, C or D or A together with B or C together with D contains an R₆O-CO group and additionally one of the groups A, B, C or D or A together with B or C together with D contains a primary, secondary or tertiary amino

55

5

- 116 -

function, whilst the nitrogen atom of this amino function is not linked to a carbon atom of an aromatic group,

10

whilst by the aryl moieties mentioned in the definition of the abovementioned groups is meant a phenyl group which may in each case be monosubstituted by R_{12} , mono-, di- or trisubstituted by R_{13} or monosubstituted by R_{12} and additionally mono- or disubstituted by R_{13} , whilst the substituents may be identical or different and

15

20

R_{12} denotes a cyano, carboxy, C_{1-4} -alkoxycarbonyl, aminocarbonyl, C_{1-4} -alkylaminocarbonyl, di- $(C_{1-4}$ -alkyl)-aminocarbonyl, C_{1-4} -alkylsulphenyl, C_{1-4} -alkylsulphinyl, C_{1-4} -alkylsulphonyl, hydroxy, C_{1-4} -alkylsulphonyloxy, trifluoromethyloxy, nitro, amino, C_{1-4} -alkylamino, di- $(C_{1-4}$ -alkyl)-amino, C_{1-4} -alkylcarbonylamino, N- $(C_{1-4}$ -alkyl)- C_{1-4} -alkylcarbonylamino, C_{1-4} -alkylsulphonylamino, N- $(C_{1-4}$ -alkyl)- C_{1-4} -alkylsulphonylamino, aminosulphonyl, C_{1-4} -alkylaminosulphonyl or di- $(C_{1-4}$ -alkyl)-aminosulphonyl group or a carbonyl group which is substituted by a 5- to 7-membered alkyleneimino group, whilst in the abovementioned 6- to 7-membered alkyleneimino groups in each case a methylene group in the 4 position may be replaced by an oxygen or sulphur atom, by a sulphinyl, sulphonyl, imino or N- $(C_{1-4}$ -alkyl)-imino group, and

25

30

35

40

R_{13} denotes a fluorine, chlorine, bromine or iodine atom, a C_{1-4} -alkyl, trifluoromethyl or C_{1-4} -alkoxy group or

two groups R_{13} , if they are bound to adjacent carbon atoms, together denote a C_{3-5} -alkylene, methylenedioxy or 1,3-butadien-1,4-ylene group,

45

the tautomers, the stereoisomers and the salts thereof.

50

55

5

- 117 -

2. Bicyclic heterocycles of general formula I according to
claim 1, wherein

10

R_a denotes a hydrogen atom,

15

R_b denotes a phenyl, benzyl or 1-phenylethyl group wherein the
phenyl nucleus is substituted in each case by the groups R_1 to
 R_3 , whilst

20

R_1 and R_2 , which may be identical or different, each denote
a hydrogen, fluorine, chlorine, bromine or iodine atom,

25

a methyl, ethyl, hydroxy, methoxy, ethoxy, amino, cyano,
vinyl or ethynyl group,

an aryl, aryloxy, arylmethyl or arylmethoxy group,

30

a methyl or methoxy group substituted by 1 to 3 fluorine
atoms or

35

R_1 together with R_2 , if they are bound to adjacent carbon
atoms, denote a $-\text{CH}=\text{CH}-\text{CH}=\text{CH}-$, $-\text{CH}=\text{CH}-\text{NH}$ or $-\text{CH}=\text{N}-\text{NH}$ group
and

40

R_3 denotes a hydrogen, fluorine, chlorine or bromine atom,

R_c and R_d in each case denote a hydrogen atom,

X denotes a nitrogen atom,

45

A denotes an $-\text{O}-\text{C}_{1-4}-$ alkylene, $-\text{O}-\text{C}_{4-7}-$ cycloalkylene, $-\text{O}-\text{C}_{1-3}-$ al-
kylene- $\text{C}_{3-7}-$ cycloalkylene, $-\text{O}-\text{C}_{4-7}-$ cycloalkylene- $\text{C}_{1-3}-$ alkylene or
 $-\text{O}-\text{C}_{1-3}-$ alkylene- $\text{C}_{3-7}-$ cycloalkylene- $\text{C}_{1-3}-$ alkylene group, whilst
the oxygen atom of the abovementioned groups in each case is
linked to the bicyclic heteroaromatic ring,

50

55

5

- 118 -

10

an -O-C₁₋₄-alkylene group which is substituted from position 2 onwards by a hydroxy group, whilst the oxygen atom of the abovementioned-O-C₁₋₄-alkylene groups in each case is linked to the bicyclic heteroaromatic ring, or

15

an oxygen atom, this being linked to a carbon atom of the group B,

20

B denotes an R₆O-CO-alkylene-NR₅, (R₇O-PO-OR₈)-alkylene-NR₅ or (R₇O-PO-R₈)-alkylene-NR₅ group wherein in each case the alkylene moiety, which is straight-chained and contains 1 to 4 carbon atoms, may additionally be substituted by one or two C₁₋₂-alkyl groups or by an R₆O-CO or R₆O-CO-C₁₋₂-alkyl group, whilst

25

R₅ denotes a hydrogen atom,

30

a C₁₋₄-alkyl group which may be substituted by an R₆O-CO group,

35

a C₂₋₄-alkyl group which is substituted from position 2 by a hydroxy or C₁₋₄-alkoxy group,

a C₃₋₆-cycloalkyl or C₃₋₆-cycloalkyl-C₁₋₃-alkyl group,

40

R₆, R₇ and R₈, which may be identical or different, in each case denote a hydrogen atom,

45

a C₁₋₆-alkyl group which may be substituted from position 2 onwards by a hydroxy, C₁₋₄-alkoxy or di-(C₁₋₄-alkyl)-amino group or by a 4- to 7-membered alkyleneimino group, whilst in the abovementioned 6- to 7-membered alkyleneimino groups in each case a methylene group in the 4 position may be replaced by an oxygen atom or by an N-(C₁₋₂-alkyl)-imino group,

50

a C₄₋₆-cycloalkyl group,

55

5

- 119 -

a C₃₋₅-alkenyl or C₃₋₅-alkynyl group, whilst the unsaturated moiety may not be linked to the oxygen atom,

10

a C₃₋₆-cycloalkyl-C₁₋₄-alkyl, aryl, aryl-C₁₋₄-alkyl or R₆CO-O-(R₆CR₂) group, whilst

15

R₆ and R₂, which may be identical or different, in each case denote a hydrogen atom or a C₁₋₄-alkyl group and

20

R₆ denotes a C₁₋₄-alkyl, C₃₋₆-cycloalkyl, C₁₋₄-alkoxy or C₅₋₆-cycloalkoxy group,

and R₂ denotes a C₁₋₄-alkyl group,

25

a 4- to 7-membered alkyleneimino group which is substituted by an R₆O-CO, R₆O-CO-C₁₋₄-alkyl or bis-(R₆O-CO)-C₁₋₄-alkyl group wherein R₆ is as hereinbefore defined,

30

a 4- to 7-membered alkyleneimino group which is substituted by two R₆O-CO or R₆O-CO-C₁₋₄-alkyl groups wherein R₆ is as hereinbefore defined,

35

a piperazino or homopiperazino group which is substituted in the 4 position by the group R₁₀ and additionally at a cyclic carbon atom by an R₆O-CO, R₆O-CO-C₁₋₄-alkyl or bis-(R₆O-CO)-C₁₋₄-alkyl group wherein R₆ is as hereinbefore defined and

40

R₁₀ denotes a hydrogen atom, a methyl or ethyl group,

45

a piperazino or homopiperazino group which is substituted in the 4 position by the group R₁₀ and is additionally substituted at cyclic carbon atoms by two R₆O-CO or R₆O-CO-C₁₋₄-alkyl groups wherein R₆ and R₁₀ are as hereinbefore defined,

50

a piperazino or homopiperazino group which in each case is substituted in the 4 position by an R₆O-CO-C₁₋₄-alkyl, bis-

55

5

- 120 -

(R₆O-CO)-C₁₋₄-alkyl, (R₇O-PO-OR₈)-C₁₋₄-alkyl or (R₇O-PO-R₉)-C₁₋₄-alkyl group wherein R₆ to R₉ are as hereinbefore defined,

10

a piperazino or homopiperazino group which is substituted in the 4 position by an R₆O-CO-C₁₋₄-alkyl or bis-(R₆O-CO)-C₁₋₄-alkyl group and is additionally substituted at cyclic carbon atoms by one or two R₆O-CO or R₆O-CO-C₁₋₄-alkyl groups wherein R₆ is as hereinbefore defined,

15

a morpholino or homomorpholino group which is substituted in each case by an R₆O-CO, R₆O-CO-C₁₋₄-alkyl, or bis-(R₆O-CO)-C₁₋₄-alkyl group wherein R₆ is as hereinbefore defined,

20

a morpholino or homomorpholino group which is substituted by two R₆O-CO or R₆O-CO-C₁₋₄-alkyl groups wherein R₆ is as hereinbefore defined,

25

a pyrrolidinyl, piperidinyl or hexahydroazepinyl group substituted in the 1 position by the group R₁₀, whilst the abovementioned 5- to 7-membered rings in each case are additionally substituted at a carbon atom by an R₆O-CO, R₆O-CO-C₁₋₄-alkyl or bis-(R₆O-CO)-C₁₋₄-alkyl group wherein R₆ and R₁₀ are as hereinbefore defined,

30

35

a pyrrolidinyl, piperidinyl or hexahydroazepinyl group substituted in the 1 position by the group R₁₀, whilst the abovementioned 5- to 7-membered rings are in each case additionally substituted at carbon atoms by two R₆O-CO or R₆O-CO-C₁₋₄-alkyl groups wherein R₆ and R₁₀ are as hereinbefore defined,

40

a pyrrolidinyl, piperidinyl or hexahydroazepinyl group substituted in the 1 position by an R₆O-CO-C₁₋₄-alkyl, bis-(R₆O-CO)-C₁₋₄-alkyl, (R₇O-PO-OR₈)-C₁₋₄-alkyl or (R₇O-PO-R₉)-C₁₋₄-alkyl group wherein R₆ to R₉ are as hereinbefore defined,

45

a pyrrolidinyl, piperidinyl or hexahydroazepinyl group substituted in the 1 position by an R₆O-CO-C₁₋₄-alkyl or bis-

50

55

(R₆O-CO)-C₁₋₄-alkyl group, whilst the abovementioned 5- to 7-membered rings are in each case additionally substituted at carbon atoms by one or two R₆O-CO or R₆O-CO-C₁₋₄-alkyl groups wherein R₆ is as hereinbefore defined,

a 2-oxo-morpholino group which may be substituted by 1 to 4 C₁₋₂-alkyl groups,

a 2-oxo-morpholinyl group which is substituted in the 4 position by a hydrogen atom, by a C₁₋₄-alkyl or R₆O-CO-C₁₋₄-alkyl group, whilst R₆ is as hereinbefore defined and the abovementioned 2-oxo-morpholinyl groups in each case are linked to a carbon atom of the group A,

an R₁₁NR₅ group wherein R₅ is as hereinbefore defined and

R₁₁ denotes a 2-oxo-tetrahydrofuran-3-yl, 2-oxo-tetrahydrofuran-4-yl, 2-oxo-tetrahydropyran-3-yl, 2-oxo-tetrahydropyran-4-yl or 2-oxo-tetrahydropyran-5-yl group optionally substituted by one or two methyl groups,

or A and B together denote a hydrogen atom,

a C₁₋₄-alkoxy group,

a C₂₋₄-alkoxy group which is substituted from position 2 by a hydroxy, C₁₋₄-alkoxy, amino, C₁₋₄-alkylamino, di-(C₁₋₄-alkyl)-amino, pyrrolidino, piperidino, morpholino, piperazino or 4-(C₁₋₄-alkyl)-piperazino group,

a C₁₋₄-alkoxy group which is substituted by a pyrrolidinyl or piperidinyl group substituted in the 1 position by the group R₁₀, whilst R₁₀ is as hereinbefore defined,

a C₁₋₄-alkoxy group which is substituted by an R₆O-CO group, whilst R₆ is as hereinbefore defined,

5

- 122 -

a C₄₋₇-cycloalkoxy or C₃₋₇-cycloalkyl-C₁₋₄-alkoxy group,

10

C denotes an -O-C₁₋₄-alkylene, -O-C₄₋₇-cycloalkylene, -O-C₁₋₃-alkylene-C₃₋₇-cycloalkylene, -O-C₄₋₇-cycloalkylene-C₁₋₃-alkylene or -O-C₁₋₃-alkylene-C₃₋₇-cycloalkylene-C₁₋₃-alkylene group, whilst the oxygen atom of the abovementioned group in each case is

15

linked to the bicyclic heteroaromatic ring,

an -O-C₂₋₄-alkylene group which is substituted from position 2 onwards by a hydroxy group, whilst the oxygen atom of the abovementioned-O-C₂₋₄-alkylene groups in each case is linked to the bicyclic heteroaromatic ring, or

20

an oxygen atom, which is linked to a carbon atom of the group D,

25

D denotes an R₆O-CO-alkylene-NR₅, (R₇O-PO-OR₈)-alkylene-NR₅ or (R₇O-PO-R₈)-alkylene-NR₅ group wherein in each case the alkylene moiety, which is straight-chained and contains 1 to 4 carbon atoms, may additionally be substituted by one or two C₁₋₂-alkyl groups or by an R₆O-CO or R₆O-CO-C₁₋₂-alkyl group, whilst R₅ to R₈ are as hereinbefore defined,

30

35

a 4- to 7-membered alkyleneimino group which is substituted by an R₆O-CO, R₆O-CO-C₁₋₄-alkyl or bis-(R₆O-CO)-C₁₋₄-alkyl group wherein R₆ is as hereinbefore defined,

40

a 4- to 7-membered alkyleneimino group which is substituted by two R₆O-CO or R₆O-CO-C₁₋₄-alkyl groups wherein R₆ is as hereinbefore defined,

45

a piperazino or homopiperazino group which is substituted in the 4 position by the group R₁₀ and additionally at a cyclic carbon atom by an R₆O-CO, R₆O-CO-C₁₋₄-alkyl or bis-(R₆O-CO)-C₁₋₄-alkyl group wherein R₆ and R₁₀ are as hereinbefore defined,

50

55

5
10 a piperazino or homopiperazino group which is substituted in the 4 position by the group R_{10} and is additionally substituted at cyclic carbon atoms by two R_6 O-CO or R_6 O-CO- $C_{1,4}$ -alkyl groups wherein R_6 and R_{10} are as hereinbefore defined,

15 a piperazino or homopiperazino group which is substituted in each case in the 4 position by an R_6 O-CO- $C_{1,4}$ -alkyl, bis- $(R_6$ O-CO)- $C_{1,4}$ -alkyl, $(R_6$ O-PO-OR₈)- $C_{1,4}$ -alkyl or $(R_6$ O-PO- R_9)- $C_{1,4}$ -alkyl group wherein R_6 to R_9 are as hereinbefore defined,

20 a piperazino or homopiperazino group which is substituted in the 4 position by an R_6 O-CO- $C_{1,4}$ -alkyl or bis- $(R_6$ O-CO)- $C_{1,4}$ -alkyl group and is additionally substituted at cyclic carbon atoms by one or two R_6 O-CO or R_6 O-CO- $C_{1,4}$ -alkyl groups wherein R_6 is as
25 hereinbefore defined,

30 a morpholino or homomorpholino group which is substituted in each case by an R_6 O-CO, R_6 O-CO- $C_{1,4}$ -alkyl, or bis- $(R_6$ O-CO)- $C_{1,4}$ -alkyl group wherein R_6 is as hereinbefore defined,

35 a morpholino or homomorpholino group which is substituted by two R_6 O-CO or R_6 O-CO- $C_{1,4}$ -alkyl groups wherein R_6 is as hereinbefore defined,

40 a pyrrolidinyl, piperidinyl or hexahydroazepinyl group substituted in the 1 position by the group R_{10} , whilst the abovementioned 5- to 7-membered rings in each case are additionally substituted at a carbon atom by an R_6 O-CO, R_6 O-CO- $C_{1,4}$ -alkyl or bis- $(R_6$ O-CO)- $C_{1,4}$ -alkyl group wherein R_6 and R_{10} are as hereinbefore defined,

45 a pyrrolidinyl, piperidinyl or hexahydroazepinyl group substituted in the 1 position by the group R_{10} , whilst the abovementioned 5- to 7-membered rings are in each case additionally substituted at carbon atoms by two R_6 O-CO or R_6 O-CO- $C_{1,4}$ -alkyl
50 groups wherein R_6 and R_{10} are as hereinbefore defined,

5

- 124 -

10

a pyrrolidinyl, piperidinyl or hexahydroazepinyl group substituted in the 1 position by an $R_6O-CO-C_{1-4}$ -alkyl, bis- $(R_6O-CO)-C_{1-4}$ -alkyl, $(R_6O-PO-OR_6)-C_{1-4}$ -alkyl or $(R_6O-PO-R_6)-C_{1-4}$ -alkyl group wherein R_6 to R_9 are as hereinbefore defined,

15

a pyrrolidinyl, piperidinyl or hexahydroazepinyl group substituted in the 1 position by an $R_6O-CO-C_{1-4}$ -alkyl or bis- $(R_6O-CO)-C_{1-4}$ -alkyl group, whilst the abovementioned 5- to 7-membered rings are in each case additionally substituted at carbon atoms by one or two R_6O-CO or $R_6O-CO-C_{1-4}$ -alkyl groups wherein R_6 is as hereinbefore defined,

20

a 2-oxo-morpholino group which may be substituted by 1 to 4 C_{1-2} -alkyl groups,

25

a 2-oxo-morpholinyl group which is substituted in the 4 position by a hydrogen atom, by a C_{1-4} -alkyl or $R_6O-CO-C_{1-4}$ -alkyl group, whilst R_6 is as hereinbefore defined and the abovementioned 2-oxo-morpholinyl groups are in each case linked to a carbon atom of the group C,

30

an $R_{11}NR_5$ group wherein R_5 and R_{11} are as hereinbefore defined, or

35

C and D together denote a hydrogen atom,

40

a C_{1-4} -alkoxy group,

45

a C_{2-4} -alkoxy group which is substituted from position 2 by a hydroxy, C_{1-4} -alkoxy, amino, C_{1-4} -alkylamino, di- $(C_{1-4}$ -alkyl)-amino, pyrrolidino, piperidino, morpholino, piperazino or 4- $(C_{1-4}$ -alkyl)-piperazino group,

50

a C_{1-4} -alkoxy group which is substituted by a pyrrolidinyl or piperidinyl group substituted in the 1 position by the group R_{10} , whilst R_{10} is as hereinbefore defined,

55

5
10 a C₁₋₄-alkoxy group which is substituted by an R₆O-CO group,
whilst R₆ is as hereinbefore defined,

a C₄₋₇-cycloalkoxy or C₃₋₇-cycloalkyl-C₁₋₄-alkoxy group

15 with the proviso that at least one of the groups B or D or A
together with B or C together with D contains an optionally
substituted 2-oxo-morpholinyl group, a (R₇O-PO-OR₈) or
(R₇O-PO-R₈) group, or

20 that at least one of the groups B or D contains an optionally
substituted 2-oxo-tetrahydrofuran-3-yl, 2-oxo-tetrahydrofuran-
4-yl, 2-oxo-tetrahydropyran-3-yl, 2-oxo-tetrahydropyran-4-yl or
2-oxo-tetrahydropyran-5-yl group, or

25 that at least one of the groups A, B, C or D or A together with
B or C together with D contains an R₆O-CO group and additional-
ly one of the groups A, B, C or D or A together with B or C
30 together with D contains a primary, secondary or tertiary amino
function, whilst the nitrogen atom of this amino function is
not linked to a carbon atom of an aromatic group,

35 whilst by the aryl moieties mentioned in the definition of the
abovementioned groups is meant a phenyl group which in each
case may be monosubstituted by R₁₂, mono- or disubstituted by
R₁₃, or monosubstituted by R₁₂ and additionally mono- or disub-
40 stituted by R₁₃, whilst the substituents may be identical or
different and

45 R₁₂ denotes a cyano, C₁₋₂-alkoxycarbonyl, aminocarbonyl,
C₁₋₂-alkylaminocarbonyl, di-(C₁₋₂-alkyl)-aminocarbonyl,
C₁₋₂-alkylsulphenyl, C₁₋₂-alkylsulphinyl, C₁₋₂-alkylsulphonyl,
hydroxy, nitro, amino, C₁₋₄-alkylamino or di-(C₁₋₄-alkyl)-amino
group and

50 R₁₃ denotes a fluorine, chlorine, bromine or iodine atom, a
C₁₋₂-alkyl, trifluoromethyl or C₁₋₂-alkoxy group or

5

- 126 -

10

two groups $R_{1,3}$, if they are bound to adjacent carbon atoms, together denote a $C_{3,5}$ -alkylene, methylenedioxy or 1,3-butadien-1,4-ylene group,

15

the tautomers, stereoisomers and salts thereof.

2. Bicyclic heterocycles of general formula I according to claim 1, wherein

20

R_a denotes a hydrogen atom,

25

R_b denotes a phenyl, benzyl or 1-phenylethyl group wherein the phenyl nucleus is substituted in each case by the groups R_1 to R_3 , whilst

30

R_1 and R_2 , which may be identical or different, each denote a hydrogen, fluorine, chlorine or bromine atom,

a methyl, trifluoromethyl, methoxy, ethynyl or cyano group and

35

R_3 denotes a hydrogen atom,

R_c and R_d in each case denote a hydrogen atom,

40

X denotes a nitrogen atom,

45

A denotes an $-O-C_{1-4}$ -alkylene or $-O-CH_2-CH(OH)-CH_2$ group, whilst the oxygen atom of the abovementioned groups in each case is linked to the bicyclic heteroaromatic ring,

50

B denotes an R_eO-CO -alkylene- NR_f group wherein the alkylene moiety, which is straight-chained and contains 1 or 2 carbon atoms, may additionally be substituted by an R_eO-CO or R_eO-CO -methyl group, whilst

55

5

- 127 -

R_5 denotes a hydrogen atom,

10

a C_{1-2} -alkyl group which may be substituted by an R_6 O-CO group,

15

a C_{2-4} -alkyl group which is substituted from position 2 onwards by a hydroxy group,

a C_{3-6} -cycloalkyl or C_{3-6} -cycloalkylmethyl group and

20

R_6 denotes a hydrogen atom,

25

a C_{1-6} -alkyl, cyclopentyl, cyclopentylmethyl, cyclohexyl, cyclohexylmethyl, phenyl, benzyl, 5-indanyl or R_6 CO-O-
(R_6 CR₂) group, whilst

R_6 denotes a hydrogen atom or a C_{1-4} -alkyl group,

30

R_7 denotes a hydrogen atom and

R_8 denotes a C_{1-4} -alkyl, cyclopentyl, cyclohexyl,
 C_{1-4} -alkoxy, cyclopentyloxy or cyclohexyloxy group,

35

a pyrrolidino or piperidino group which is substituted by an R_6 O-CO or R_6 O-CO- C_{1-2} -alkyl group wherein R_6 is as hereinbefore defined,

40

a pyrrolidino or piperidino group which is substituted by two R_6 O-CO or R_6 O-CO- C_{1-2} -alkyl groups wherein R_6 is as hereinbefore defined,

45

a piperazino group which is substituted in the 4 position by the group R_{10} and additionally at a cyclic carbon atom by an R_6 O-CO or R_6 O-CO- C_{1-2} -alkyl group wherein R_6 is as hereinbefore defined and

50

R_{10} denotes a hydrogen atom, a methyl or ethyl group,

55

5

10

a piperazino group which is substituted in the 4 position by an $R_6O-CO-C_{1-4}$ -alkyl, bis- $(R_6O-CO)-C_{1-4}$ -alkyl, $(R_7O-PO-OR_8)$ -methyl or $(R_7O-PO-R_8)$ -methyl group wherein R_6 is as hereinbefore defined,

15

R_7 and R_8 , which may be identical or different, in each case denote a hydrogen atom, a methyl, ethyl, phenyl, benzyl, 5-indanyl or $R_9CO-O-(R_6CR_6)$ group, whilst

20

R_6 to R_9 are as hereinbefore defined,

and R_9 denotes a methyl or ethyl group,

25

a piperazino group which is substituted in the 4 position by an $R_6O-CO-C_{1-2}$ -alkyl group and additionally at a cyclic carbon atom by an R_6O-CO or $R_6O-CO-C_{1-2}$ -alkyl group wherein R_6 is as hereinbefore defined,

30

a morpholino group which is substituted by an R_6O-CO or $R_6O-CO-C_{1-2}$ -alkyl group, whilst R_6 is as hereinbefore defined,

35

a pyrrolidinyl or piperidinyl group substituted in the 1 position by an $R_6O-CO-C_{1-4}$ -alkyl, bis- $(R_6O-CO)-C_{1-4}$ -alkyl, $(R_7O-PO-OR_8)$ -methyl or $(R_7O-PO-R_8)$ -methyl group wherein R_6 to R_8 are as hereinbefore defined,

40

a 2-oxo-morpholino group which may be substituted by 1 or 2 methyl groups,

45

a 2-oxo-morpholinyl group which is substituted in the 4 position by a methyl, ethyl or $R_6O-CO-C_{1-2}$ -alkyl group, whilst R_6 is as hereinbefore defined and the abovementioned 2-oxo-morpholinyl groups in each case are linked to a carbon atom of the group A,

50

a $R_{11}N(C_{1-2}$ -alkyl) group wherein R_{11} denotes a 2-oxo-tetrahydrofuran-3-yl or 2-oxo-tetrahydrofuran-4-yl group, or

55

A and B together denote a hydrogen atom, a methoxy, ethoxy or 2-methoxy-ethoxy group,

a C_{1-2} -alkoxy group which is substituted by an R_6O-CO group, whilst R_6 is as hereinbefore defined,

a C_{4-6} -cycloalkoxy or C_{3-6} -cycloalkyl- C_{1-3} -alkoxy group,

C denotes an $-O-C_{1-4}$ -alkylene or $-O-CH_2-CH(OH)-CH_2$ group, whilst the oxygen atom of the abovementioned groups in each case is linked to the bicyclic heteroaromatic ring,

D denotes an R_4O-CO -alkylene- NR_5 group wherein the alkylene moiety, which is straight-chained and contains 1 or 2 carbon atoms, may additionally be substituted by an R_6O-CO or R_6O-CO -methyl group, whilst R_5 and R_6 are as hereinbefore defined,

a pyrrolidino or piperidino group which is substituted by an R_6O-CO or $R_6O-CO-C_{1-2}$ -alkyl group wherein R_6 is as hereinbefore defined,

a pyrrolidino or piperidino group which is substituted by two R_6O-CO or $R_6O-CO-C_{1-2}$ -alkyl groups wherein R_6 is as hereinbefore defined,

a piperazino group which is substituted in the 4 position by the group R_{10} and additionally at a cyclic carbon atom by an R_6O-CO or $R_6O-CO-C_{1-2}$ -alkyl group wherein R_6 and R_{10} are as hereinbefore defined,

a piperazino group which is substituted in the 4 position by an $R_6O-CO-C_{1-4}$ -alkyl, bis- $(R_6O-CO)-C_{1-4}$ -alkyl, $(R_6O-PO-OR_6)$ -methyl or $(R_6O-PO-R_6)$ -methyl group wherein R_6 to R_9 are as hereinbefore defined,

5

- 130 -

10

a piperazino group which is substituted in the 4 position by an $R_6O-CO-C_{1-2}$ -alkyl group and additionally at a cyclic carbon atom by an R_6O-CO or $R_6O-CO-C_{1-2}$ -alkyl group wherein R_6 is as hereinbefore defined,

15

a morpholino group which is substituted by an R_6O-CO or $R_6O-CO-C_{1-2}$ -alkyl group, whilst R_6 is as hereinbefore defined,

20

a pyrrolidinyl or piperidinyl group substituted in the 1 position by an $R_6O-CO-C_{1-4}$ -alkyl, bis- $(R_6O-CO)-C_{1-4}$ -alkyl, $(R_7O-PO-OR_8)$ -methyl or $(R_7O-PO-R_9)$ -methyl group wherein R_6 to R_9 are as hereinbefore defined,

25

a 2-oxo-morpholino group which may be substituted by 1 or 2 methyl groups,

30

a 2-oxo-morpholinyl group which is substituted in the 4 position by a methyl, ethyl or $R_6O-CO-C_{1-2}$ -alkyl group, whilst R_6 is as hereinbefore defined and the abovementioned 2-oxo-morpholinyl groups are in each case linked to a carbon atom of the group C, or

35

a $R_{11}N(C_{1-2}-alkyl)$ group wherein R_{11} denotes a 2-oxo-tetrahydrofuran-3-yl or 2-oxo-tetrahydrofuran-4-yl group, or

40

C and D together denote a hydrogen atom, a methoxy, ethoxy or 2-methoxy-ethoxy group,

45

a C_{1-2} -alkoxy group which is substituted by an R_6O-CO group, whilst R_6 is as hereinbefore defined,

a C_{4-6} -cycloalkoxy or C_{3-6} -cycloalkyl- C_{1-3} -alkoxy group

50

with the proviso that at least one of the groups B or D or A together with B or C together with D contains an optionally substituted 2-oxo-morpholinyl group, a $(R_7O-PO-OR_8)$ or $(R_7O-PO-R_9)$ group, or

55

5

- 131 -

10

15

that at least one of the groups A, B, C or D or A together with B or C together with D contains an R_6O-CO group and additionally one of the groups A, B, C or D or A together with B or C together with D contains a primary, secondary or tertiary amino function, whilst the nitrogen atom of this amino function is not linked to a carbon atom of an aromatic group,

the tautomers, stereoisomers and salts thereof.

20

3. Bicyclic heterocycles of general formula I according to claim 1, wherein

25

R_a denotes a hydrogen atom,

30

R_b denotes a phenyl, benzyl or 1-phenylethyl group wherein the phenyl nucleus is substituted in each case by the groups R_1 to R_3 , whilst

35

R_1 and R_2 , which may be identical or different, each denote a hydrogen, fluorine, chlorine or bromine atom,

a methyl, trifluoromethyl, methoxy, ethynyl or cyano group and

R_3 denotes a hydrogen atom,

40

R_c and R_d in each case denote a hydrogen atom,

X denotes a nitrogen atom,

45

A denotes an $-O-C_{1-4}$ -alkylene or $-O-CH_2-CH(OH)-CH_2$ group, whilst the oxygen atom of the abovementioned groups in each case is linked to the bicyclic heteroaromatic ring,

50

B denotes an R_6O-CO -alkylene- NR_5 group wherein the alkylene moiety, which is straight-chained and contains 1 or 2 carbon

55

5

- 132 -

atoms, may additionally be substituted by an R_6O-CO or R_6O-CO-
methyl group, whilst

10

R_5 denotes a hydrogen atom,

15

a C_{1-2} -alkyl group which may be substituted by an R_6O-CO
group,

20

a C_{2-4} -alkyl group which is substituted from position 2
onwards by a hydroxy group,

a C_{3-6} -cycloalkyl or C_{3-6} -cycloalkylmethyl group and

25

R_6 denotes a hydrogen atom,

a C_{1-6} -alkyl, cyclopentyl, cyclopentylmethyl, cyclohexyl,
cyclohexylmethyl, phenyl, benzyl, 5-indanyl or R_6CO-O-
(R_6CR_2) group, whilst

30

R_8 denotes a hydrogen atom or a C_{1-4} -alkyl group,

R_7 denotes a hydrogen atom and

35

R_9 denotes a C_{1-4} -alkyl, cyclopentyl, cyclohexyl,
 C_{1-4} -alkoxy, cyclopentyloxy or cyclohexyloxy group,

40

a pyrrolidino or piperidino group which is substituted by an
 R_6O-CO or $R_6O-CO-C_{1-2}$ -alkyl group wherein R_6 is as hereinbefore
defined,

45

a pyrrolidino or piperidino group which is substituted by two
 R_6O-CO or $R_6O-CO-C_{1-2}$ -alkyl groups wherein R_6 is as hereinbefore
defined,

50

a piperazino group which is substituted in the 4 position by
the group R_{10} and additionally at a cyclic carbon atom by an

55

5

- 133 -

R_4O-CO or $R_4O-CO-C_{1-2}$ -alkyl group wherein R_4 is as hereinbefore defined and

10

R_{10} denotes a hydrogen atom, a methyl or ethyl group,

15

a piperazino group which is substituted in the 4 position by an $R_4O-CO-C_{1-4}$ -alkyl, bis- $(R_4O-CO)-C_{1-4}$ -alkyl, $(R_4O-PO-OR_8)$ -methyl or $(R_4O-PO-R_9)$ -methyl group wherein R_4 is as hereinbefore defined,

20

R_7 and R_8 , which may be identical or different, in each case denote a hydrogen atom, a methyl, ethyl, phenyl, benzyl, 5-indanyl or $R_9CO-O-(R_4CR_7)$ group, whilst

25

R_6 to R_9 are as hereinbefore defined,

and R_5 denotes a methyl or ethyl group,

30

a piperazino group which is substituted in the 4 position by an $R_4O-CO-C_{1-2}$ -alkyl group and is additionally substituted at a cyclic carbon atom by an R_4O-CO or $R_4O-CO-C_{1-2}$ -alkyl group wherein R_4 is as hereinbefore defined,

35

a morpholino group which is substituted by an R_4O-CO or $R_4O-CO-C_{1-2}$ -alkyl group, whilst R_4 is as hereinbefore defined,

40

a pyrrolidinyl or piperidinyl group substituted in the 1 position by an $R_4O-CO-C_{1-4}$ -alkyl, bis- $(R_4O-CO)-C_{1-4}$ -alkyl, $(R_4O-PO-OR_8)$ -methyl or $(R_4O-PO-R_9)$ -methyl group wherein R_4 to R_9 are as hereinbefore defined,

45

a 2-oxo-morpholino group which may be substituted by 1 or 2 methyl groups,

50

a 2-oxo-morpholinyl group which is substituted in the 4 position by a methyl, ethyl or $R_4O-CO-C_{1-2}$ -alkyl group, whilst R_4 is as hereinbefore defined and the abovementioned 2-oxo-morpho-

55

linyl groups in each case are linked to a carbon atom of the group A, or

a $R_{11}N(C_{1-2}\text{-alkyl})$ group wherein R_{11} denotes a 2-oxo-tetrahydrofuran-3-yl or 2-oxo-tetrahydrofuran-4-yl group, and

C and D together denote a hydrogen atom, a methoxy, ethoxy, 2-methoxy-ethoxy, C_{4-6} -cycloalkoxy or C_{3-6} -cycloalkyl- C_{1-3} -alkoxy group,

the tautomers, the stereoisomers and the salts thereof.

4. Bicyclic heterocycles of general formula I according to claim 1, wherein

R_a denotes a hydrogen atom,

R_b denotes a phenyl, benzyl or 1-phenylethyl group wherein the phenyl nucleus is substituted in each case by the groups R_1 to R_3 , whilst

R_1 and R_2 , which may be identical or different, each denote a hydrogen, fluorine, chlorine or bromine atom,

a methyl, trifluoromethyl, methoxy, ethynyl or cyano group and

R_3 denotes a hydrogen atom,

R_c and R_d in each case denote a hydrogen atom,

X denotes a nitrogen atom,

A and B together denote a hydrogen atom, a methoxy, ethoxy, 2-methoxy-ethoxy, C_{4-6} -cycloalkoxy or C_{3-6} -cycloalkyl- C_{1-3} -alkoxy group,

5

- 135 -

10

C denotes an $-O-C_{1-4}$ -alkylene or $-O-CH_2-CH(OH)-CH_2$ group, whilst the oxygen atom of the abovementioned groups in each case is linked to the bicyclic heteroaromatic ring, and

15

D denotes an R_6O-CO -alkylene- NR_7 group wherein the alkylene moiety, which is straight-chained and contains 1 or 2 carbon atoms, may additionally be substituted by an R_6O-CO or R_6O-CO -methyl group, whilst

20

R_5 denotes a hydrogen atom,

a C_{1-2} -alkyl group which may be substituted by an R_6O-CO group,

25

a C_{2-4} -alkyl group which is substituted from position 2 by a hydroxy group,

30

a C_{1-6} -cycloalkyl or C_{1-6} -cycloalkylmethyl group and

35

R_6 denotes a hydrogen atom,

a C_{1-6} -alkyl, cyclopentyl, cyclopentylmethyl, cyclohexyl, cyclohexylmethyl, phenyl, benzyl, 5-indanyl or $R_6CO-O-(R_6CR_7)$ group, whilst

40

R_8 denotes a hydrogen atom or a C_{1-4} -alkyl group,

R_7 denotes a hydrogen atom and

45

R_9 denotes a C_{1-4} -alkyl, cyclopentyl, cyclohexyl, C_{1-4} -alkoxy, cyclopentyloxy or cyclohexyloxy group,

50

a pyrrolidino or piperidino group which is substituted by an R_6O-CO or $R_6O-CO-C_{1-2}$ -alkyl group wherein R_6 is as hereinbefore defined,

55

5

- 136 -

10

a pyrrolidino or piperidino group which is substituted by two R_6O-CO or $R_6O-CO-C_{1,2}$ -alkyl groups wherein R_6 is as hereinbefore defined,

15

a piperazino group which is substituted in the 4 position by the group R_{10} and additionally at a cyclic carbon atom by an R_6O-CO or $R_6O-CO-C_{1,2}$ -alkyl group wherein R_6 is as hereinbefore defined and

20

R_{10} denotes a hydrogen atom, a methyl or ethyl group,

25

a piperazino group which is substituted in the 4 position by an $R_6O-CO-C_{1,4}$ -alkyl, bis- $(R_6O-CO)-C_{1,4}$ -alkyl, $(R_7O-PO-OR_8)$ -methyl or $(R_7O-PO-R_9)$ -methyl group wherein R_6 is as hereinbefore defined,

30

R_7 and R_8 , which may be identical or different, in each case denote a hydrogen atom, a methyl, ethyl, phenyl, benzyl, 5-indanyl or $R_5CO-O-(R_5CR_6)$ group, whilst

R_6 to R_9 are as hereinbefore defined,

and R_5 denotes a methyl or ethyl group,

35

a piperazino group which is substituted in the 4 position by an $R_6O-CO-C_{1,2}$ -alkyl group and is additionally substituted at a cyclic carbon atom by an R_6O-CO or $R_6O-CO-C_{1,2}$ -alkyl group wherein R_6 is as hereinbefore defined,

40

a morpholino group which is substituted by an R_6O-CO or $R_6O-CO-C_{1,2}$ -alkyl group, whilst R_6 is as hereinbefore defined,

45

a pyrrolidinyl or piperidinyl group substituted in the 1 position by an $R_6O-CO-C_{1,4}$ -alkyl, bis- $(R_6O-CO)-C_{1,4}$ -alkyl, $(R_7O-PO-OR_8)$ -methyl or $(R_7O-PO-R_9)$ -methyl group wherein R_6 to R_9 are as hereinbefore defined,

50

55

a 2-oxo-morpholino group which may be substituted by 1 or 2 methyl groups,

a 2-oxo-morpholinyl group which is substituted in the 4 position by a methyl, ethyl or $R_6O-CO-C_{1-2}$ -alkyl group, whilst R_6 is as hereinbefore defined and the abovementioned 2-oxo-morpholinyl groups are in each case linked to a carbon atom of the group C, or

a $R_{11}N(C_{1-2}$ -alkyl) group wherein R_{11} denotes a 2-oxo-tetrahydrofuran-3-yl or 2-oxo-tetrahydrofuran-4-yl group,

the tautomers, stereoisomers and salts thereof.

5. Bicyclic heterocycles of general formula I according to claim 1, wherein

R_a denotes a hydrogen atom,

R_b denotes a phenyl group wherein the phenyl nucleus is substituted in each case by the groups R_1 to R_5 , whilst

R_1 and R_2 , which may be identical or different, each denote a hydrogen, fluorine, chlorine or bromine atom and

R_3 denotes a hydrogen atom,

R_c and R_d in each case denote a hydrogen atom,

X denotes a nitrogen atom,

A denotes an $-O-C_{1-4}$ -alkylene or $-O-CH_2-CH(OH)-CH_2$ group, whilst the oxygen atom of the abovementioned groups in each case is linked to the bicyclic heteroaromatic ring,

B denotes an $R_6O-CO-CH_2-NR_5$ group wherein

5
10 R_5 denotes a hydrogen atom or a methyl group which may be substituted by an R_4O-CO group, or

a C_{2-4} -alkyl group substituted from position 2 onwards by a hydroxy group, and

15 R_6 denotes a hydrogen atom, a methyl or ethyl group,

a pyrrolidino or piperidino group which is substituted by an R_4O-CO group, whilst R_6 is as hereinbefore defined,

20 a piperazino group which is substituted in the 4 position by an $R_4O-CO-CH_2$ or bis- $(R_4O-CO)-C_{1-3}$ -alkyl group, whilst R_6 is as hereinbefore defined,

25 a pyrrolidinyl or piperidinyl group substituted in the 1 position by an $R_4O-CO-CH_2$ group, whilst R_6 is as hereinbefore defined,

30 a 2-oxo-morpholino group which may be substituted by one or two methyl groups, or

35 a $R_{11}N(C_{1-2}\text{-alkyl})$ group wherein R_{11} denotes a 2-oxo-tetrahydrofuran-3-yl or 2-oxo-tetrahydrofuran-4-yl group, and

40 C and D together denote a methoxy, C_{4-6} -cycloalkoxy or C_{3-6} -cycloalkylmethoxy group,

the tautomers, stereoisomers and salts thereof.

45 7. Bicyclic heterocycles of general formula I according to claim 1, wherein

R_a denotes a hydrogen atom,

50 R_b denotes a phenyl group wherein the phenyl nucleus is substituted in each case by the groups R_1 to R_7 , whilst

5
10 R_1 and R_2 , which may be identical or different, each denote a hydrogen, fluorine, chlorine or bromine atom and

R_3 denotes a hydrogen atom,

15 R_4 and R_5 in each case denote a hydrogen atom,

X denotes a nitrogen atom,

20 A and B together denote a C_{4-6} -cycloalkoxy or C_{3-6} -cycloalkyl-methoxy group,

25 C denotes an $-O-CH_2CH_2$ group, whilst the oxygen atom of the abovementioned group is linked to the bicyclic heteroaromatic ring,

D denotes an $R_6O-CO-CH_2-NR_7$ group wherein

30 R_7 denotes a C_{2-4} -alkyl group substituted from position 2 onwards by a hydroxy group, and

35 R_6 denotes a methyl or ethyl group,

a 2-oxo-morpholino group which may be substituted by one or two methyl groups, or

40 a $R_{11}N(C_{1-2}$ -alkyl) group wherein R_{11} denotes a 2-oxo-tetrahydrofuran-3-yl or 2-oxo-tetrahydrofuran-4-yl group,

the tautomers, stereoisomers and salts thereof.

45 8. The following bicyclic heterocycles of general formula I according to claim 1:

50 (1) 4-(3-chloro-4-fluorophenylamino)-6-{3-[4-(methoxycarbonylmethyl)-1-piperazinyl]propyloxy}-7-methoxy-quinazoline,

5

- 140 -

10

(2) 4-[(3-bromophenyl)amino]-6-(2-{4-[(ethoxycarbonyl)methyl]-piperazin-1-yl}ethoxy)-7-methoxy-quinazoline,

15

(3) (S)-4-[(3-bromophenyl)amino]-6-[3-(2-methoxycarbonyl-pyrrolidin-1-yl)propyloxy]-7-methoxy-quinazoline,

20

(4) 4-[(3-bromophenyl)amino]-6-(3-{4-[(ethoxycarbonyl)methyl]-piperazin-1-yl}-2-hydroxy-propyloxy)-7-methoxy-quinazoline,

(5) (S)-4-[(3-bromophenyl)amino]-6-({1-[(ethoxycarbonyl)methyl]-pyrrolidine-2-yl}methoxy)-7-methoxy-quinazoline and

25

(6) 4-[(3-bromophenyl)amino]-6-(2-{4-[1,2 bis(methoxycarbonyl)-ethyl]-piperazin-1-yl}ethoxy)-7-methoxy-quinazoline

and the salts thereof.

30

9. Physiologically acceptable salts of the compounds according to claims 1 to 8 with inorganic or organic acids of bases.

35

10. Pharmaceutical compositions containing a compound according to claims 1 to 8 or a physiologically acceptable salt according to claim 9 optionally together with one or more inert carriers and/or diluents.

40

11. Use of a compound according to at least one of claims 1 to 9 for preparing a pharmaceutical compositions which is suitable for treating benign or malignant tumours, for preventing and treating diseases of the airways and lungs, for treating polyps, diseases of the gastro-intestinal tract, the bile ducts and gall bladder and the kidneys and skin.

45

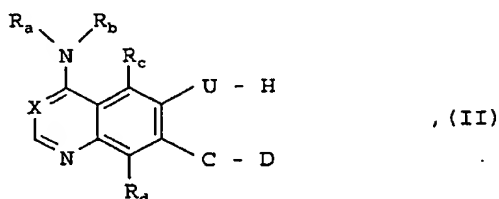
50

12. Process for preparing a pharmaceutical composition according to claim 10, characterised in that a compound according to at least one of claims 1 to 9 is incorporated in one or more inert carriers and/or diluents by a non-chemical method.

55

13. Process for preparing the compounds of general formula I according to claims 1 to 9, characterised in that

a) a compound of general formula



wherein

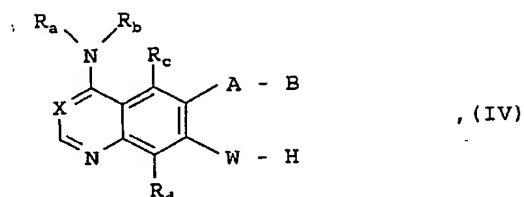
R_a to R_d , C, D and X are defined as in claims 1 to 8 and U denotes an oxygen atom or an R_eN group, whilst R_e is defined as in claims 1 to 8, is reacted with a compound of general formula



wherein

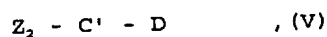
B is defined as in claims 1 to 8, A' denotes one of the optionally substituted alkylene, cycloalkylene, alkylene-cycloalkylene, cycloalkylene-alkylene or alkylene-cycloalkylene-alkylene moieties mentioned in claims 1 to 8 for the group A, which are linked to the heteroaromatic group via an oxygen atom or via an NR_e group, and Z_1 denotes a leaving group, or

b) a compound of general formula



wherein

R_a to R_d , A, B and X are defined as in claims 1 to 8 and W denotes an oxygen atom or an R_eN group, whilst R_e is defined as in claims 1 to 8, is reacted with a compound of general formula



wherein

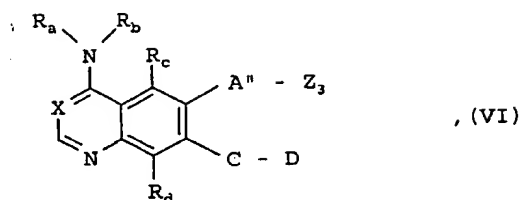
D is defined as in claims 1 to 8,

C' denotes one of the optionally substituted alkylene, cycloalkylene, alkylene-cycloalkylene, cycloalkylene-alkylene or alkylene-cycloalkylene-alkylene moieties mentioned above for the group C, which are linked to the heteroaromatic group via an oxygen atom or via an NR_e group, and Z_2 denotes a leaving group, or

c) in order to prepare a compound of general formula I wherein A is defined as in claims 1 to 8 with the exception of the oxygen atom and the $-NR_e$ group:

- 143 -

a compound of general formula



wherein

20 R_a to R_d , C, D and X are defined as in claims 1 to 8 and A'' has the meanings given for A in claims 1 to 8 with the exception of the oxygen atom and the $-NR_4$ group and Z_3 denotes a leaving group or together with a hydrogen atom of an adjacent hydrocarbon group denotes an oxygen atom, is

25 reacted with a compound of general formula

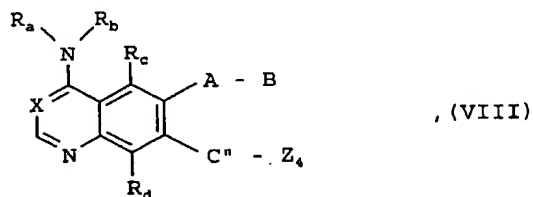


30 wherein

B is defined as in claims 1 to 8, or

35 d) in order to prepare a compound of general formula I wherein C is defined as in claims 1 to 8 with the exception of the oxygen atom and the $-NR_4$ group:

a compound of general formula



50 wherein

C'' has the meanings given for C in claims 1 to 8 with the exception of the oxygen atom and the $-NR_4$ group and

55

- 144 -

5
10
15
20
25
30
35
40
45
50
55

Z₄ denotes a leaving group or together with a hydrogen atom of an adjacent hydrocarbon group denotes an oxygen atom, is reacted with a compound of general formula

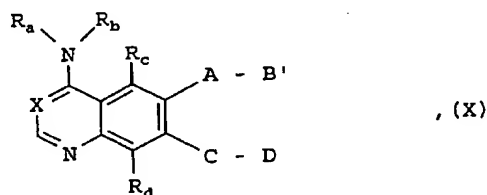


wherein

D is defined as in claims 1 to 8, or

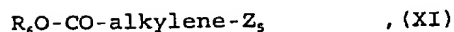
e) in order to prepare a compound of general formula I wherein B denotes an R₆O-CO-alkylene-NR₅ group wherein the alkylene moiety, which is straight-chained and contains 1 to 6 carbon atoms, may additionally be substituted by one or two C₁₋₂-alkyl groups or by an R₆O-CO or R₆O-CO-C₁₋₂-alkyl group, a piperazino or homopiperazino group substituted in the 4 position by an R₆O-CO-C₁₋₄-alkyl or bis-(R₆O-CO)-C₁₋₄-alkyl group or a pyrrolidinyl, piperidinyl or hexahydroazepinyl group substituted in the 1 position by an R₆O-CO-C₁₋₄-alkyl or bis-(R₆O-CO)-C₁₋₄-alkyl group, whilst in each case R₅ and R₆ are defined as in claims 1 to 8:

a compound of general formula



wherein

R_a to R_d, A, C, D and X are defined as in claims 1 to 8 and B' denotes an R₅NH group wherein R₅ is defined as in claims 1 to 8, a piperazino or homopiperazino group unsubstituted in the 4 position, a pyrrolidinyl, piperidinyl or hexahydroazepinyl group unsubstituted in the 1 position, is reacted with a compound of general formula



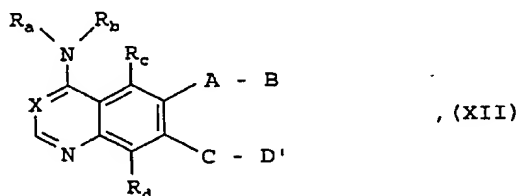
wherein

the alkylene moiety, which is straight-chained and contains 1 to 6 carbon atoms, may additionally be substituted by one or two C_{1-2} -alkyl groups or by an R_6O-CO or $R_6O-CO-C_{1-2}$ -alkyl group, whilst R_6 in each case is defined as in claims 1 to 8, and Z_5 denotes an exchangeable group, or

f) in order to prepare a compound of general formula I wherein D denotes an $R_6O-CO-alkylene-NR_5$ group wherein the alkylene moiety, which is straight-chained and contains 1 to 6 carbon atoms, may additionally be substituted by one or two C_{1-2} -alkyl groups or by an R_6O-CO or $R_6O-CO-C_{1-2}$ -alkyl group, a piperazino or homopiperazino group substituted in the 4 position by an $R_6O-CO-C_{1-4}$ -alkyl or bis- $(R_6O-CO)-C_{1-4}$ -alkyl group or

a pyrrolidinyl, piperidinyl or hexahydroazepinyl group substituted in the 1 position by an $R_6O-CO-C_{1-4}$ -alkyl or bis- $(R_6O-CO)-C_{1-4}$ -alkyl group, whilst in each case R_5 and R_6 are defined as in claims 1 to 8:

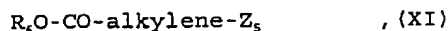
a compound of general formula



wherein

R_a to R_d , A to C and X are defined as in claims 1 to 8 and D' denotes an R_5NH group wherein R_5 is defined as in claims 1 to 8, a piperazino or homopiperazino group unsubstituted in the 4 position, a pyrrolidinyl, piperidinyl or hexahydroazepinyl

group unsubstituted in the 1 position, is reacted with a compound of general formula

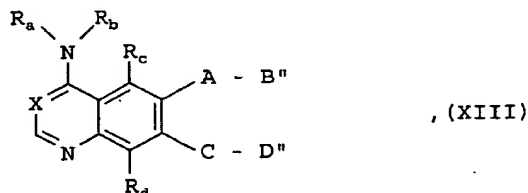


wherein

the alkylene moiety, which is straight-chained and contains 1 to 6 carbon atoms, may additionally be substituted by one or two C_{1-2} -alkyl groups or by an R_6O-CO or $R_6O-CO-C_{1-2}$ -alkyl group, whilst R_6 in each case is defined as in claims 1 to 8, and Z_5 denotes an exchangeable group, or

g) in order to prepare a compound of general formula I wherein at least one of the groups R_6 to R_8 denotes a hydrogen atom:

a compound of general formula



wherein

R_a to R_d , A, C and X are defined as in claims 1 to 8, B'' and D'' have the meanings given for B and D in claims 1 to 8, with the proviso that at least one of the groups B'' or D'' contains an R_6O-CO , $(R_7O-PO-OR_8)$ or $(R_7O-PO-R_8)$ group wherein R_7 is defined as in claims 1 to 8 and at least one of the groups R_6 to R_8 does not represent a hydrogen atom, is converted by hydrolysis, treating with acids, thermolysis or hydrogenolysis into a compound of general formula I wherein at least one of the groups R_6 to R_8 denotes a hydrogen atom,

and subsequently, if desired, a compound of general formula I thus obtained which contains a carboxy or hydroxyphosphoryl

5

group is converted by esterification into a corresponding ester of general formula I and/or

10

a compound of general formula I thus obtained wherein B or D denotes an optionally substituted N-(2-hydroxyethyl)-glycine or N-(2-hydroxyethyl)-glycine ester group is converted by cyclisation into a corresponding 2-oxo-morpholino compound, and/or

15

if necessary any protecting group used during the reactions described above is cleaved again and/or

20

if desired a compound of general formula I thus obtained is resolved into its stereoisomers and/or

25

a compound of general formula I thus obtained is converted into the salts thereof, more particularly, for pharmaceutical use, into the physiologically acceptable salts thereof.

30

35

40

45

50

55

INTERNATIONAL SEARCH REPORT

International Application No.
PCT/EP 00/02228

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D239/94 C07D215/54 C07D401/12 C07D413/12 C07D405/12
A61K31/517 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 33980 A (ZENECA) 31 October 1996 (1996-10-31) the whole document	1,8-13
X	WO 97 30035 A (ZENECA) 21 August 1997 (1997-08-21) claims; examples 13,16,22,23	1,8-13
X	WO 97 32856 A (ZENECA) 12 September 1997 (1997-09-12) claims; examples 8,9,17-20,24-27	1,8-13
X	WO 98 13354 A (ZENECA) 2 April 1998 (1998-04-02) claims; examples 3,4,9,13-15,17-23,37-58	1,8-13
	--- -/--	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

S document member of the same patent family

Date of the actual completion of the international search

10 July 2000

Date of mailing of the international search report

18/07/2000

Name and mailing address of the ISA
European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3018

Authorized officer

Francois, J

INTERNATIONAL SEARCH REPORT

Inter. Appl. No.
PCT/EP 00/02228

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 566 226 A (ZENECA) 20 October 1993 (1993-10-20) claims	1,9-13

1

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 00/02228

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9633980 A	31-10-1996	AU 699163 B	26-11-1998
		AU 5343396 A	18-11-1996
		BG 102052 A	31-08-1998
		BR 9608082 A	26-01-1999
		CA 2215732 A	31-10-1996
		CN 1182421 A	20-05-1998
		CZ 9703396 A	18-02-1998
		EP 0823900 A	18-02-1998
		HR 960204 A	31-08-1997
		HU 9802839 A	29-03-1999
		JP 11504033 T	06-04-1999
		NO 974940 A	24-10-1997
		NZ 305444 A	29-03-1999
		PL 323066 A	02-03-1998
		SK 145497 A	04-02-1998
		US 5770599 A	23-06-1998
		ZA 9603358 A	28-10-1996
WO 9730035 A	21-08-1997	AU 719434 B	11-05-2000
		AU 1729097 A	02-09-1997
		BR 9707495 A	27-07-1999
		CA 2242425 A	21-08-1997
		CN 1211239 A	17-03-1999
		CZ 9802535 A	11-11-1998
		EP 0880508 A	02-12-1998
		HU 9901155 A	28-07-1999
		NO 983687 A	13-08-1998
		PL 328310 A	18-01-1999
		SK 108798 A	11-01-1999
WO 9732856 A	12-09-1997	AU 719327 B	04-05-2000
		AU 1866497 A	22-09-1997
		CA 2244897 A	12-09-1997
		CN 1212684 A	31-03-1999
		EP 0885198 A	23-12-1998
		NO 984085 A	04-09-1998
WO 9813354 A	02-04-1998	ZA 9701747 A	27-08-1998
		AU 4561397 A	17-04-1998
		CN 1231662 A	13-10-1999
		CZ 9901039 A	16-06-1999
		EP 0929530 A	21-07-1999
		NO 991422 A	24-03-1999
		PL 332385 A	13-09-1999
		SK 38999 A	08-10-1999
EP 566226 A	20-10-1993	HU 9902850 A	28-04-2000
		AT 130000 T	15-11-1995
		AU 661533 B	27-07-1995
		AU 3101093 A	22-07-1993
		CA 2086968 A,C	21-07-1993
		CZ 282038 B	16-04-1997
		DE 69300754 D	14-12-1995
		DE 69300754 T	28-03-1996
		DK 566226 T	18-03-1996
		ES 2078798 T	16-12-1995
		FI 930208 A	21-07-1993
		GR 3018143 T	29-02-1996

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. Application No
PCT/EP 00/02228

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 566226 A		HK 36497 A	04-04-1997
		HU 63153 A	28-07-1993
		HU 9500185 A	28-07-1995
		MX 9300277 A	30-06-1994
		NO 301541 B	10-11-1997
		NZ 245662 A	26-09-1995
		RU 2127263 C	10-03-1999
		SK 1693 A	09-09-1993
		US 5457105 A	10-10-1995
		US 5616582 A	01-04-1997
		ZA 9300015 A	20-07-1993
		JP 2994165 B	27-12-1999
		JP 6073025 A	15-03-1994